Armed Forces College of Medicine

AFCM

Armed Forces College of Medicine

Neuroscience module

Clinical Integrated Cases
Session 2

Basic Science Principles for Clinical Reasoning

1- Critical thinking

2- Introduction to common forms o disease

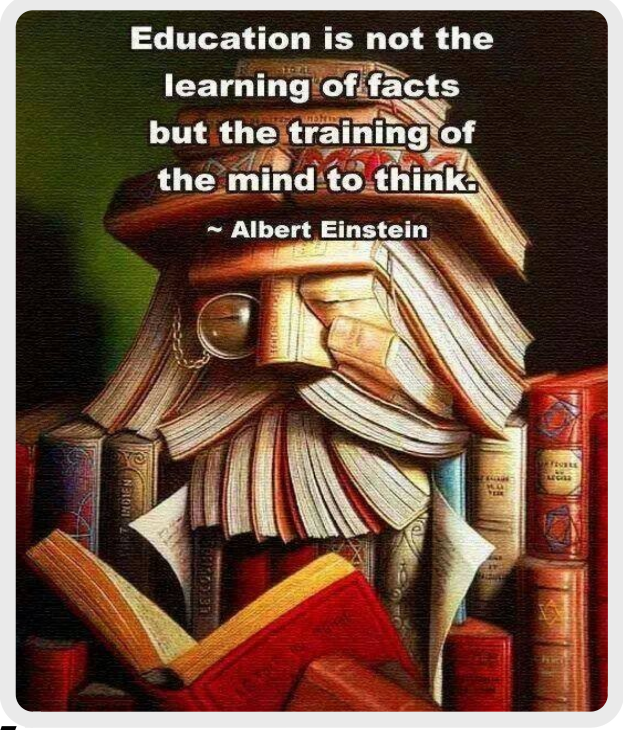
3- Problem solving: Apply basi knowledge in a realistic clinical scenario.

4- Interpersonal skills-(share and appl your knowledge)

communication…patient safety

5- Life long self-directed learning

6- Decision making



Education is not the learning of facts but the training of the mind to think.

~ Albert Einstein

Case: My hand is shaking

Case co-ordinator

Prof. Dr. Manal Hassan, Lamiaa, Mohamed Edrees, Mona Mokhtar

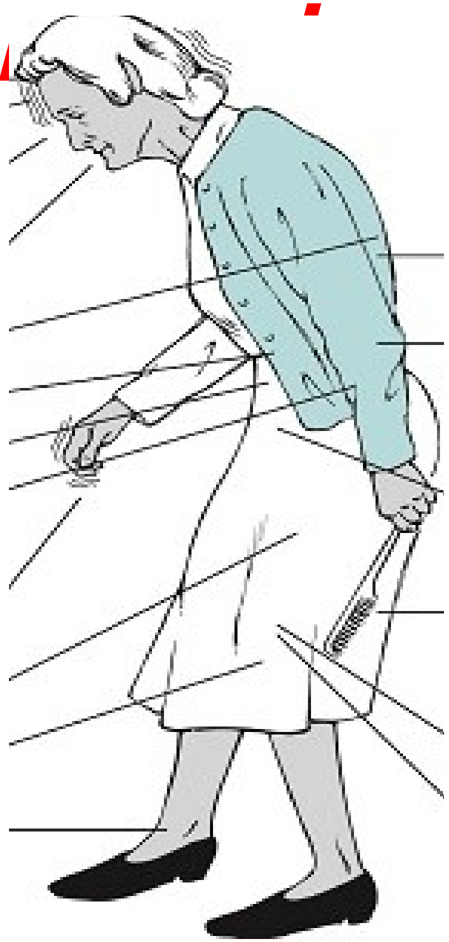
Sharing Departments

- **Neurology**
- **Physiology**
- **Biochemistry**
- **Pathology**
- **Pharmacology**

Stiff muscle with hand shaking

Samiha is a 66-year-old woman. She is a retired journalist. Samiha complains that her ***hand writing has changed and that her signature was not ap***

by the bank .



She complains that **her muscles feel stiff**, and it is taking her longer than it did to walk to the local shops.

She is anxious about these problems since she lives alone and has to do everything for herself.

She has noticed a little **shakiness** which she ascribes to anxiety.

Stiff muscle with hand shaking

She complains that she has been **sleeping poorly** and is, consequently, rather tired.

Past medical history is not significant.
She complains of **constipation that was not her habit**.
Her appetite has been good and her weight steady.
She does not smoke tobacco and drinks only occasionally.

Drug history: She has hypertension and takes **atenol**
mg daily.

Stiff muscle with hand shaking

General examination

Vital signs:
Pulse: 60/min and regular,
Blood pressure: 134/84 mmHg.
Temperature: 37.1°C
Respiratory rate: 17 cycles/min

There are no abnormalities in the cardiovascular or respiratory systems.

Stiff muscle with hand shaking

Neurologic examination

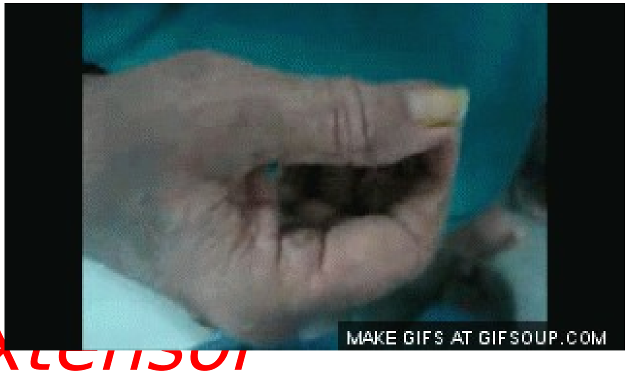
Mental state:

conscious, oriented co-operative and noticed depressed mood

Speech: Monotonus

Motor examination:

- no muscle wasting.
- **Hypertonia** ***(Rigidity)*** *affecting flexor=extensor*
- There is **a resting tremor (static)** affecting mainly her right hand **(pill rolling)**



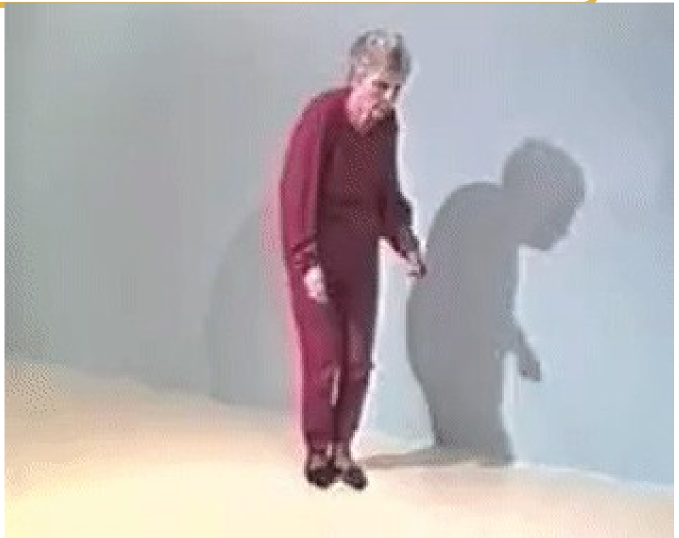
When the doctor asked her about the tremor, Samiha said that it is **suppressed when she tries to do something and *disappear during sleep*.**

Tremors are exaggerated by stress.

Stiff muscle with hand shaking

Power,
Reflexes,
Co-ordination
Sensation

are all normal



When the doctor asked Samiha to walk, her **gait** showed **short steppage slow shuffling with propulsion.** She **has difficulty in stopping and turning.**

Cranial nerves: ***Hyposmia***

Loss of habituation of glabellar reflex

Based on the History & examination:

1- a- List the patient problems

b- What is your provisional diagnosis?

C- What is the part of the neurological system affected in this patient?

Parkinson's (clinically)

History&examination

Classic **TRIAD**:

- BRADYKINESIA / slowness
- RIGIDITY / stiffness / increased tone
- TREMOR / pill rolling resting

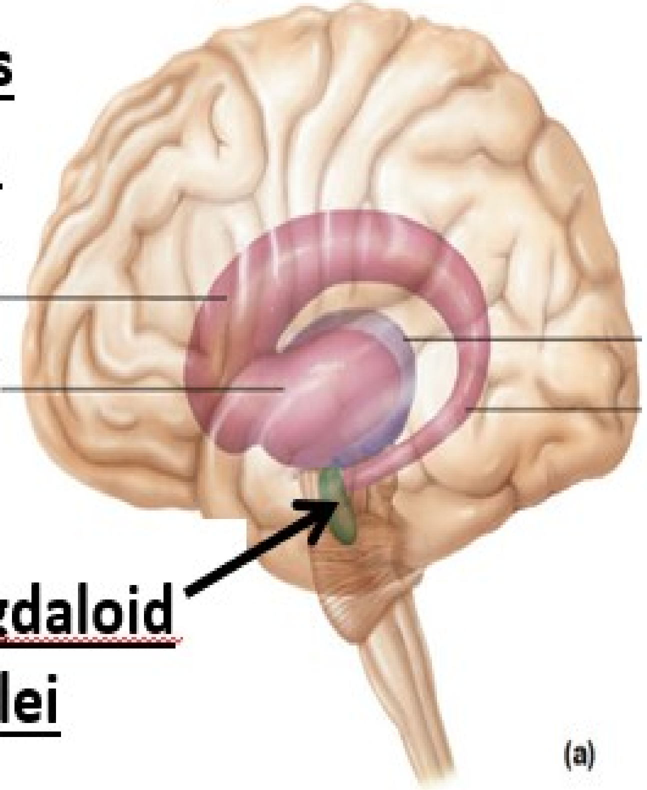
2- What are the Basal Ganglia nuclei?

BASAL NUCLEI
(BASAL GANGLIA)

They are masses of **grey matter** lying within each cerebral hemisphere near its base.

They include :

I- Corpus striatum



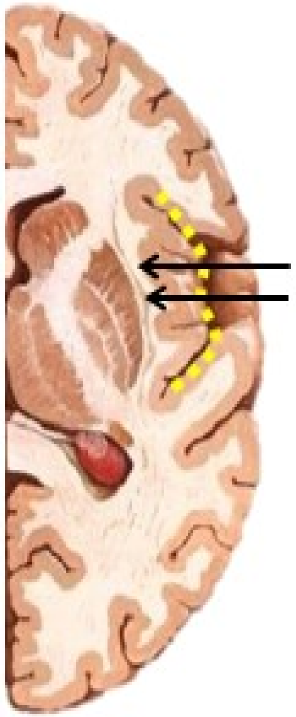
Caudate Nucleus

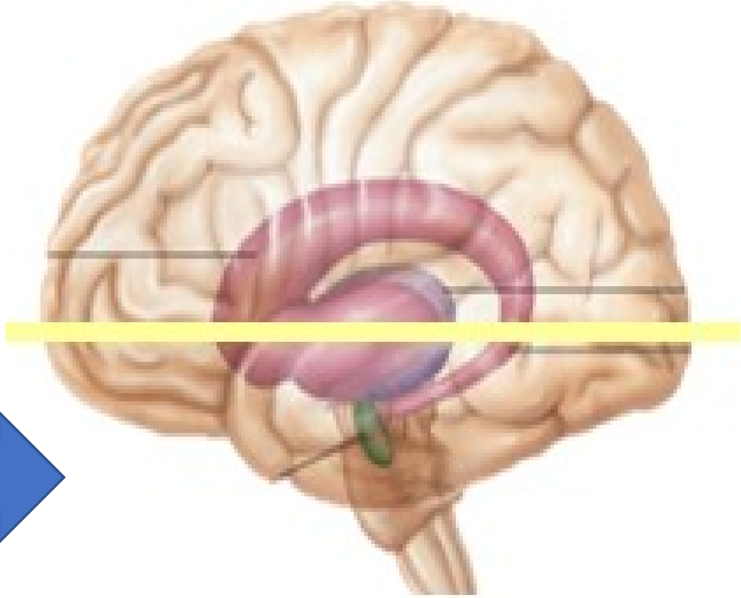
Lentiform Nucleus

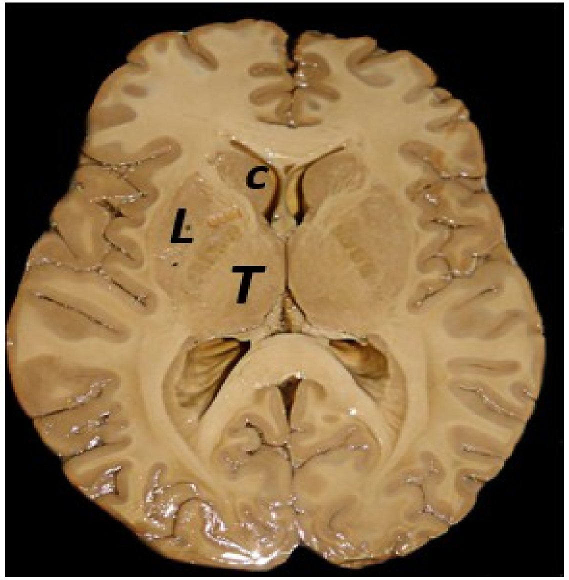
II - Amygdaloid Nuclei

III - Claustrum

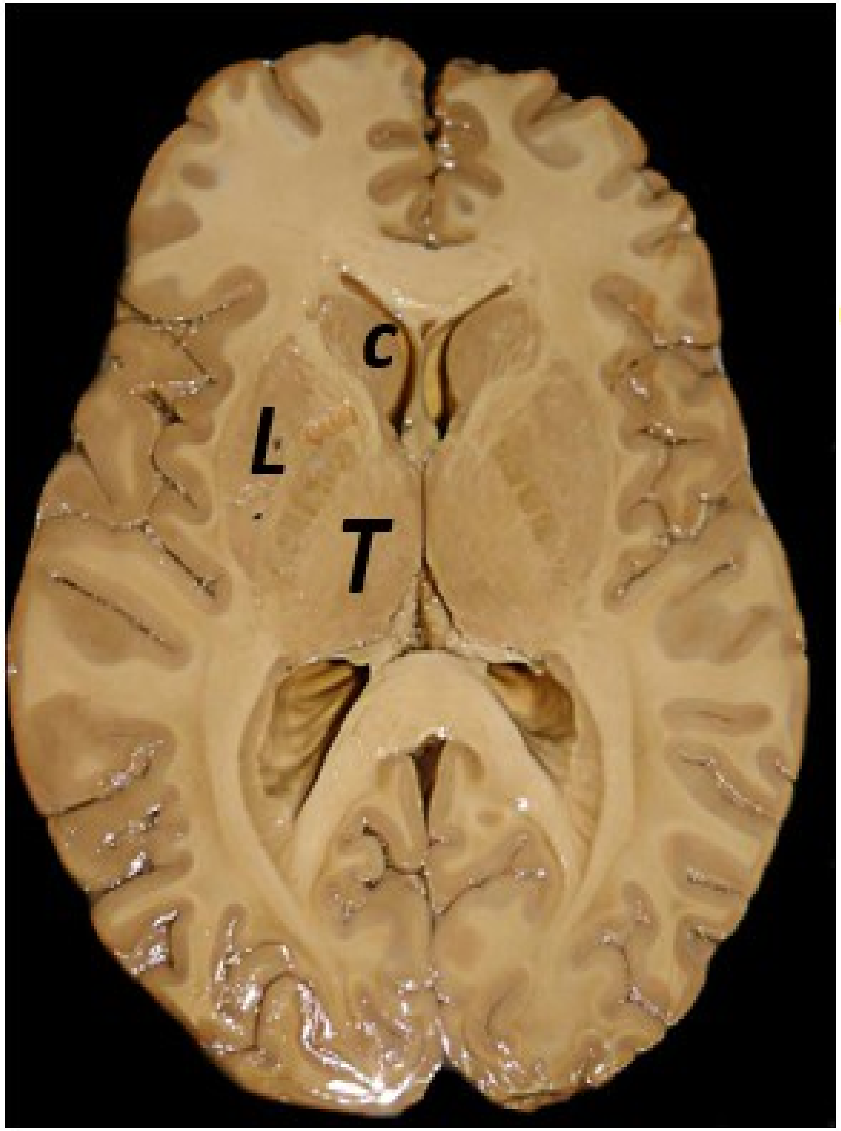
(grey matter that lies lateral to Lentiform N

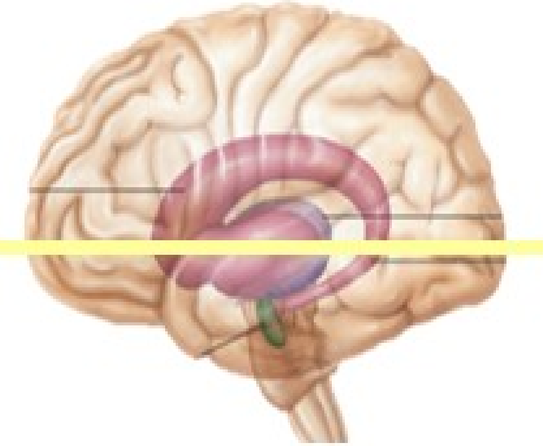


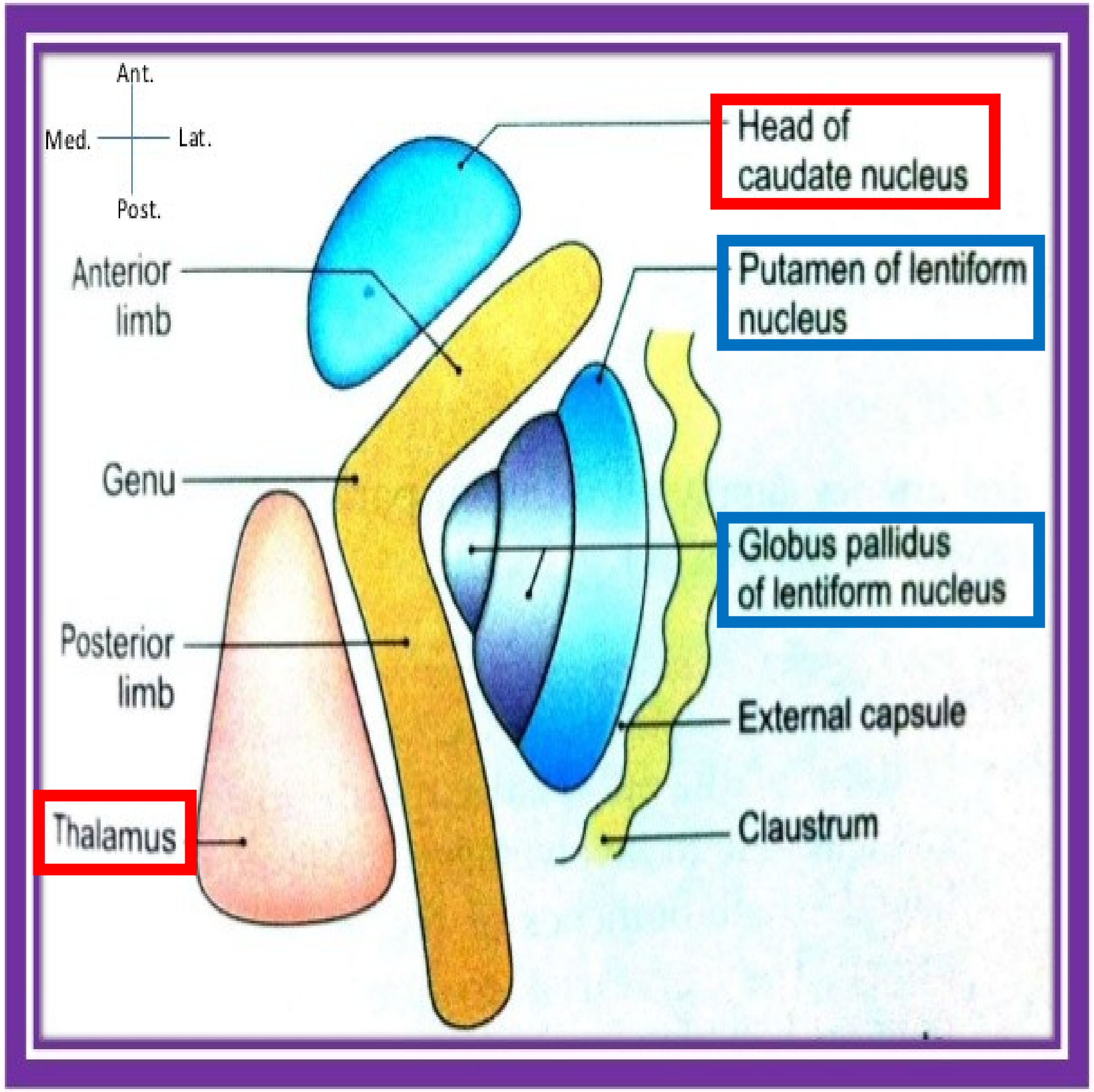




BASAL NUCLEI



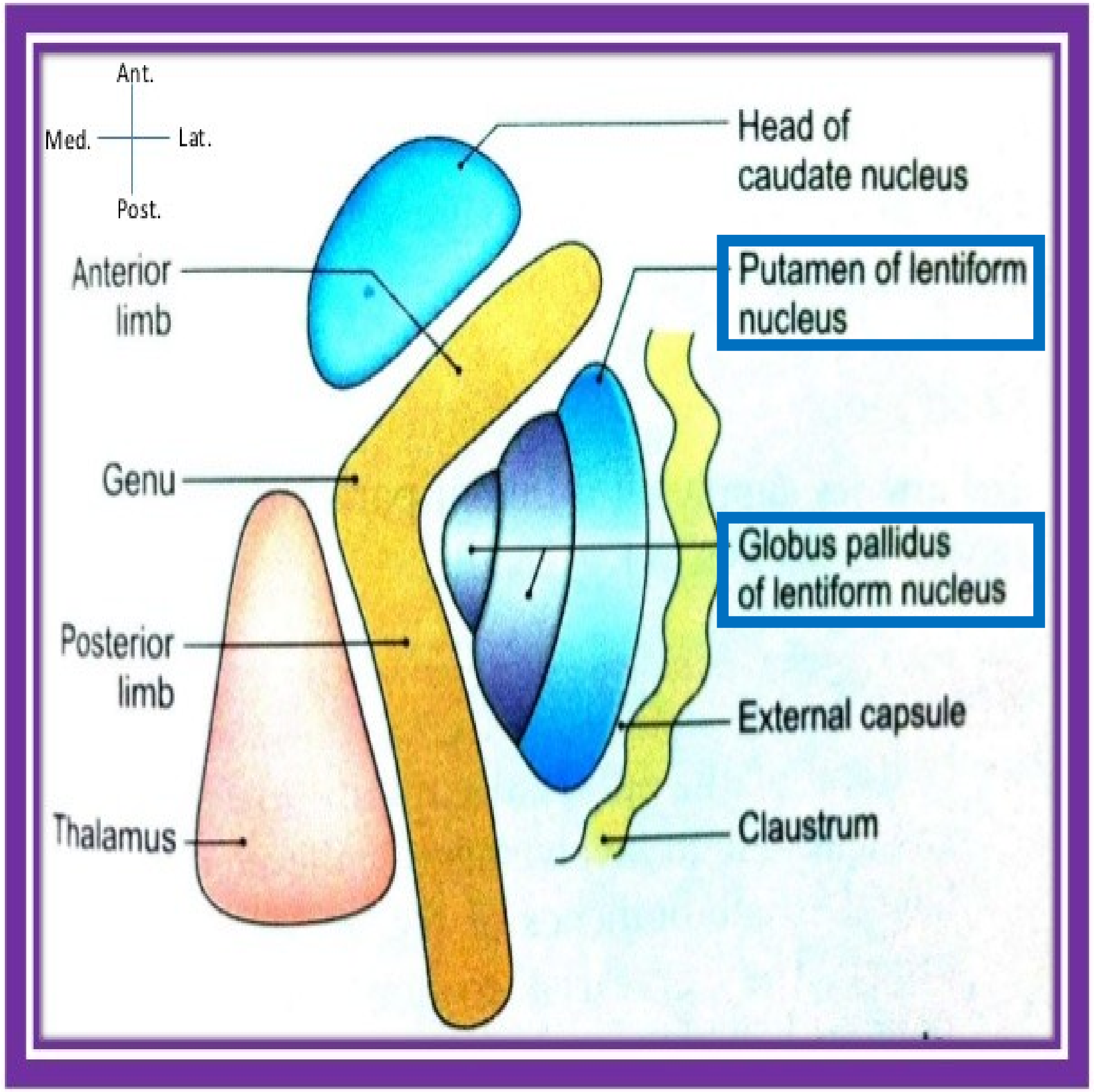




Lentiform Nucleus

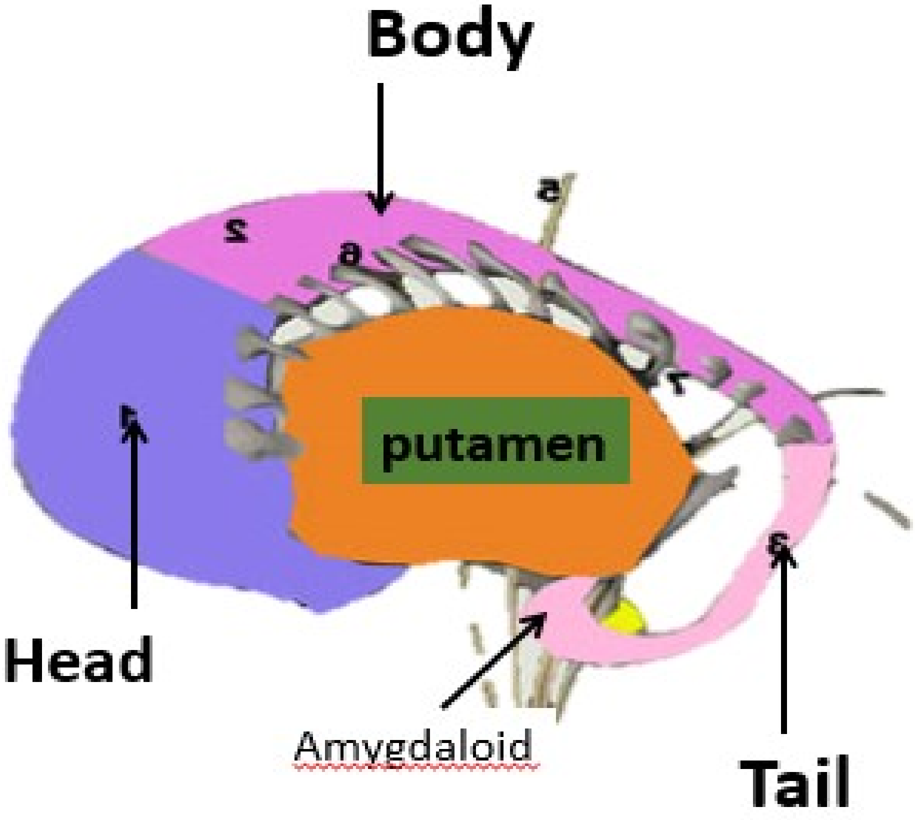
It is divided into:

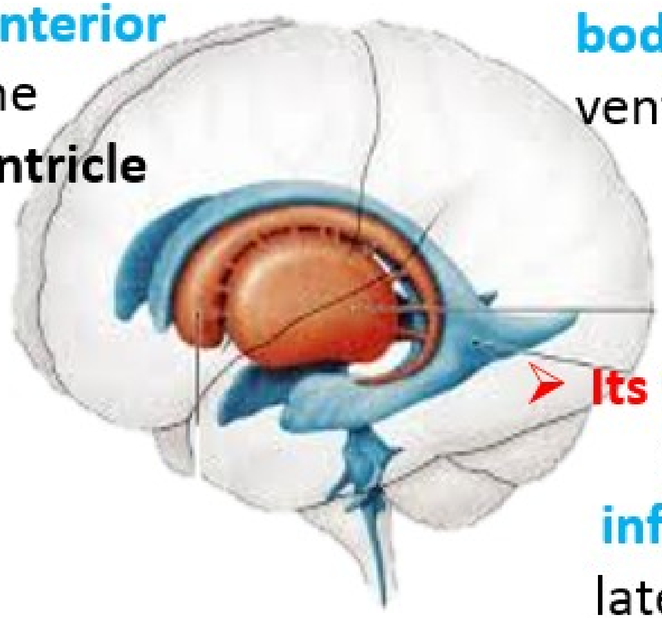
- ☐ Putamen (laterally)
- ☐ Globus Pallidus (medially): appears white due to rich myelin content.



Caudate Nucleus

- It is a **C-shaped Nucleus**
- It has a **head, body and tail**
- **The head** is continuous with **putamen of lentiform N**.
- **The tip of the tail** is continuous with the **i**.



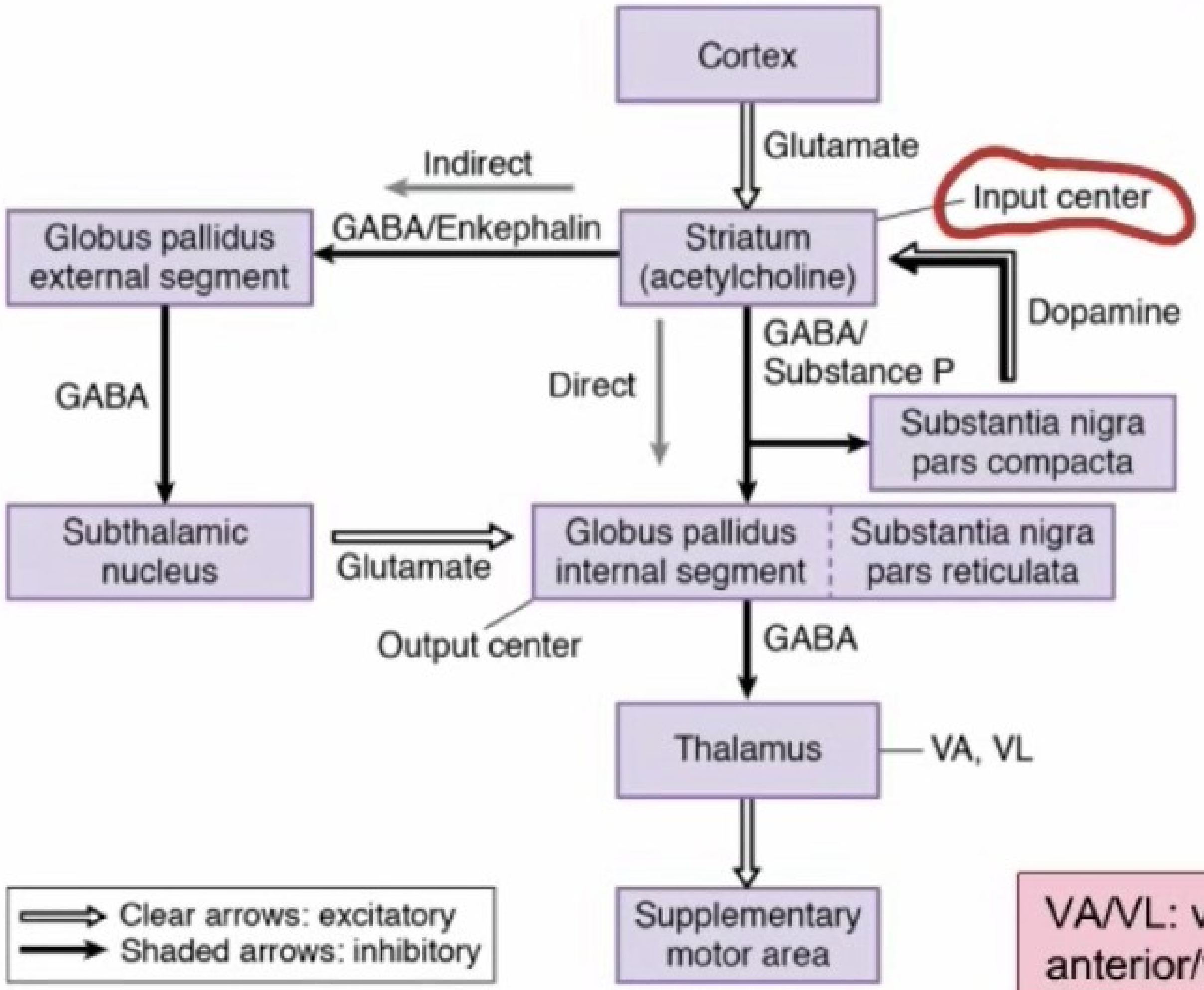


- **The head** bulges into the **anterior horn** of the **lateral ventricle**
- **Its body** lies in the **floor of the body** of lateral ventricle.
- **Its tail** lies in the roof of the **inferior horn** of lateral ventricle.

What are the connections of the basal ganglia?

Basal Ganglia Pathways

Note
Both basal ganglia pathways utilize 2 GABA neurons in series, and a “disinhibition”

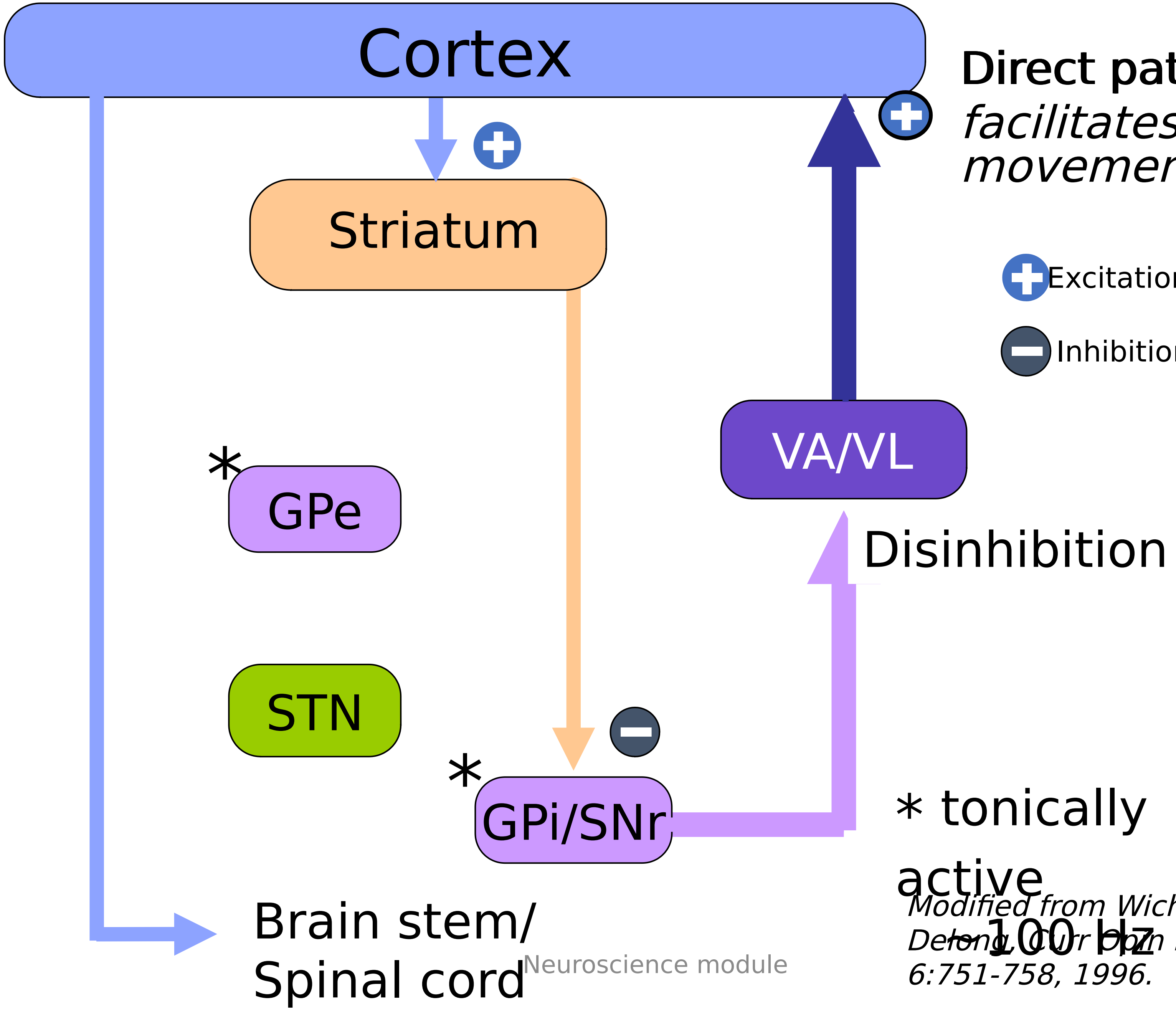


Note
- Dopamine drives the direct pathway
- Acetylcholine (ACh) drives the indirect pathway

VA/VL: ventral anterior/ventral lateral thalamic nuclei

Figure III-7-2.

Direct pathway



Cortex

⊕

Striatum

*GPe

STN

⊖

*GPi/SNr

VA/VL

⊕

Disinhibition

Brain stem/
Spinal cord

Direct pathway:
facilitates movement

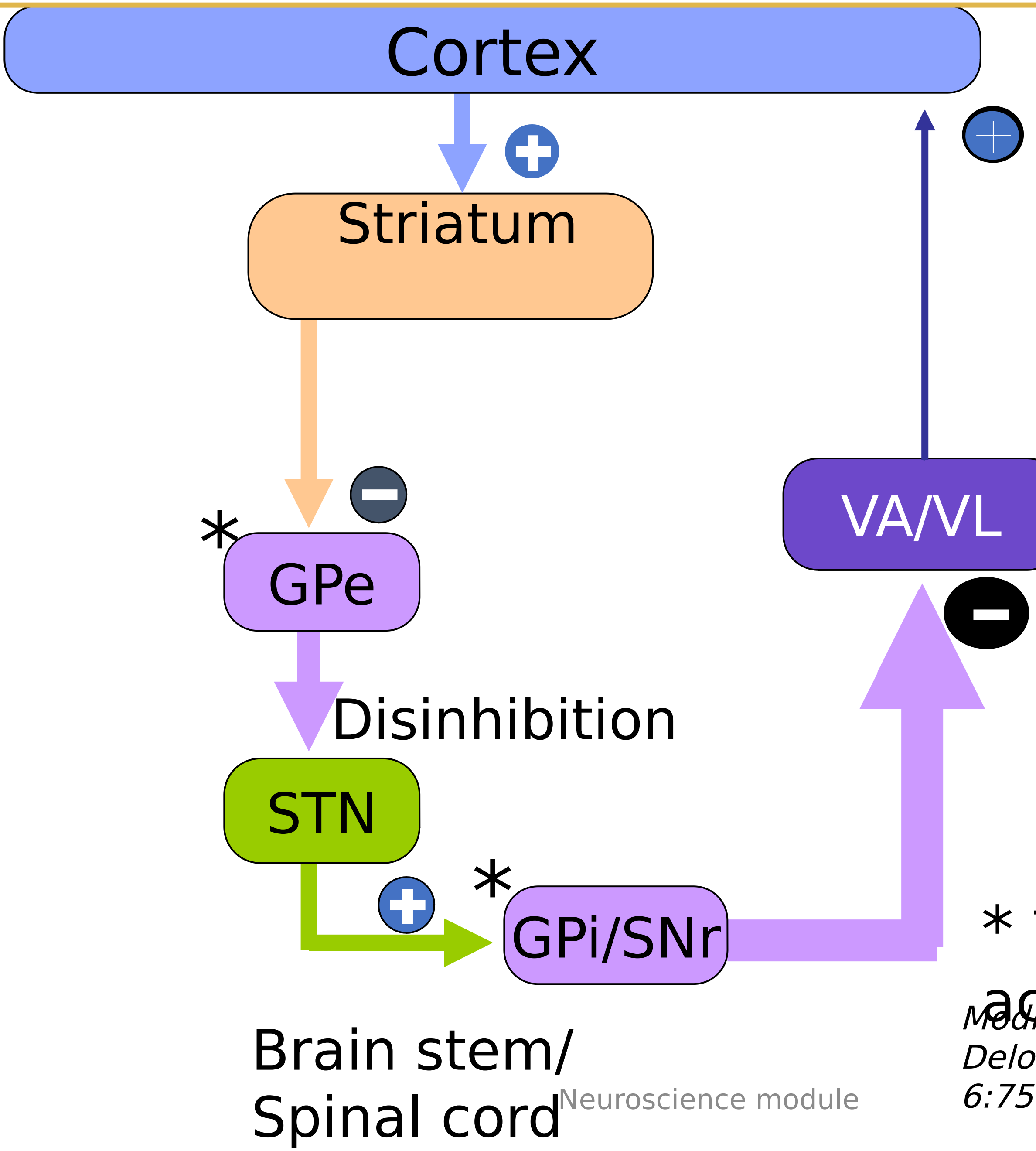
⊕ Excitation (glutamate)

⊖ Inhibition (GABA)

* tonically active
~100 Hz

Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.

Indirect pathway



Cortex

Striatum

*GPe

Disinhibition

STN

*GPi/SNr

VA/VL

Brain stem/
Spinal cord

Indirect pathway:
inhibits
movement

⊕ Excitation (glutamate)

⊖ Inhibition (GABA)

* tonically
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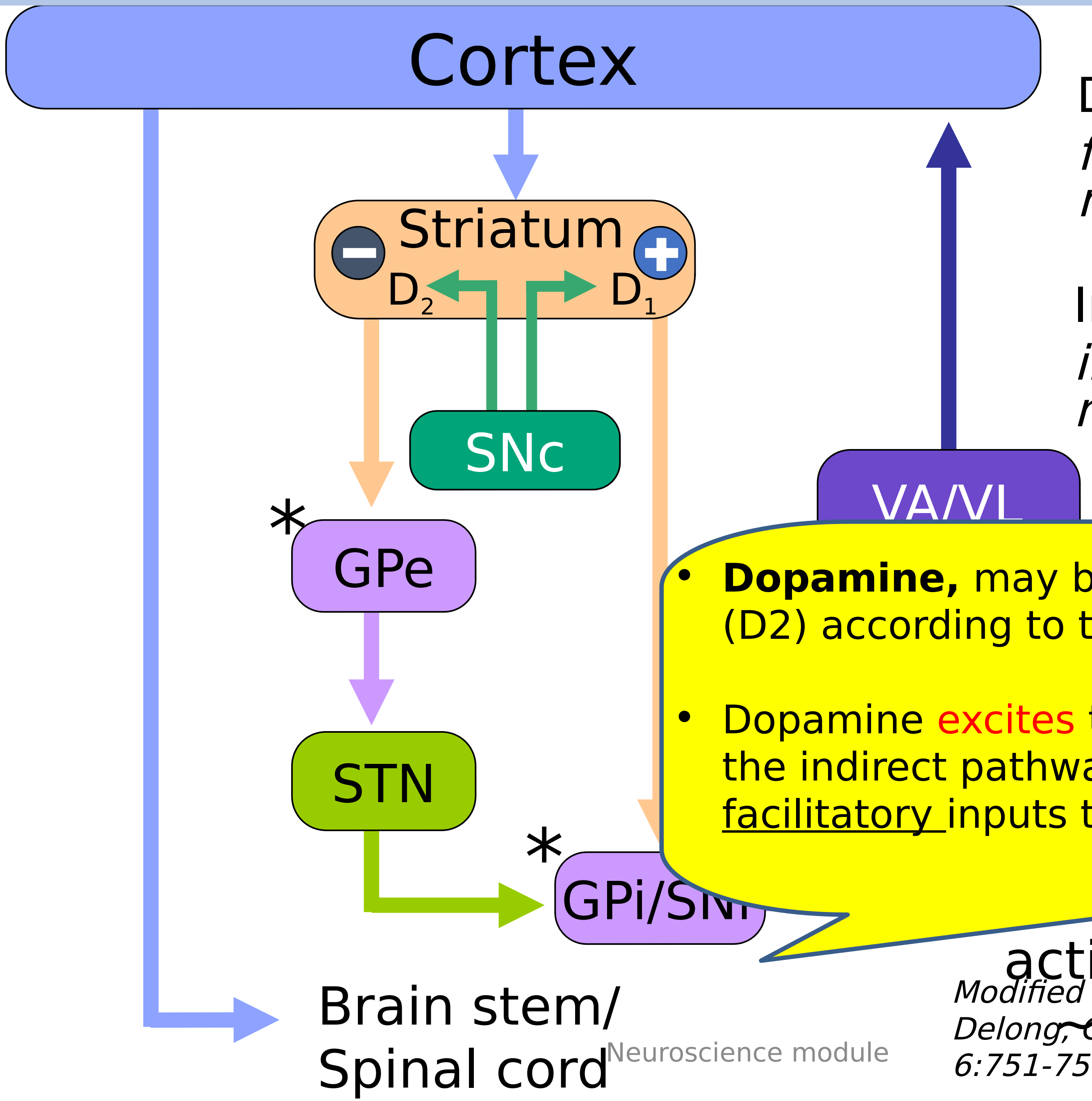
Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.

Role of dopamine in direct & indirect circuits



Direct pathway:
facilitates movement

Indirect pathway:
inhibits movement

- **Dopamine,** may be **excitatory** (D1) or inhibitory (D2) according to the receptor.
- Dopamine excites the direct pathway and inhibits the indirect pathway, with a net effect to increase facilitatory inputs to the motor regions.

active
~100 Hz

Modified from Wichmann and Delong, Curr Opin Neurobiol. 6:751-758, 1996.

Neuronal Connections & neurotransmitters of the Basal Ganglia

(1) Internal connections

(2) Cortical connections

(3) Efferent Pathways

GP

striato-nigral

Nigro-striatal

Striatum (GABA) R
SN (Dopamine) C

striato-pallidal

Striatum GABA
GP

interneurons of the striatum

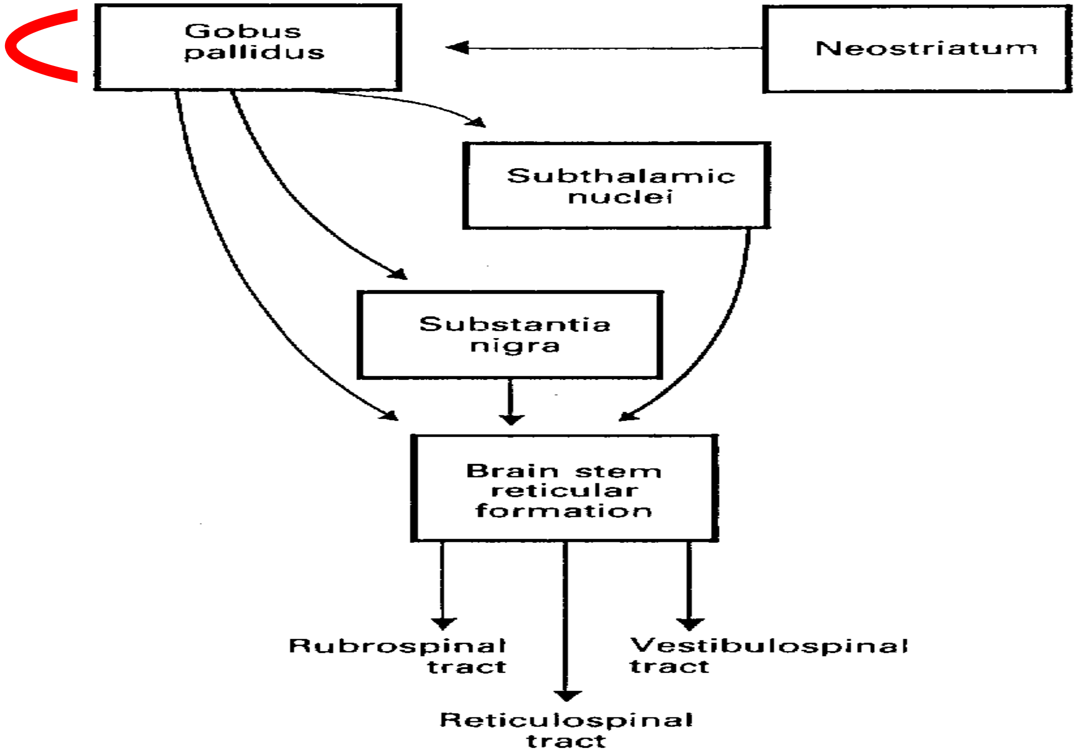
Acetyl choline

Direct pathway

Indirect pathway

Neuronal Connections & neurotransmitters of the Basal Ganglia

(3) Efferent Pathways



- **GPis GABA thalamus (**VL&VA nuclei) the cortex

- **GPes GABA subthalamus and brain stem nuclei RF extrapyramidal tracts (reticulospinal, vestibulospinal and rubrospinal) motor neurons of the spinal cord.**

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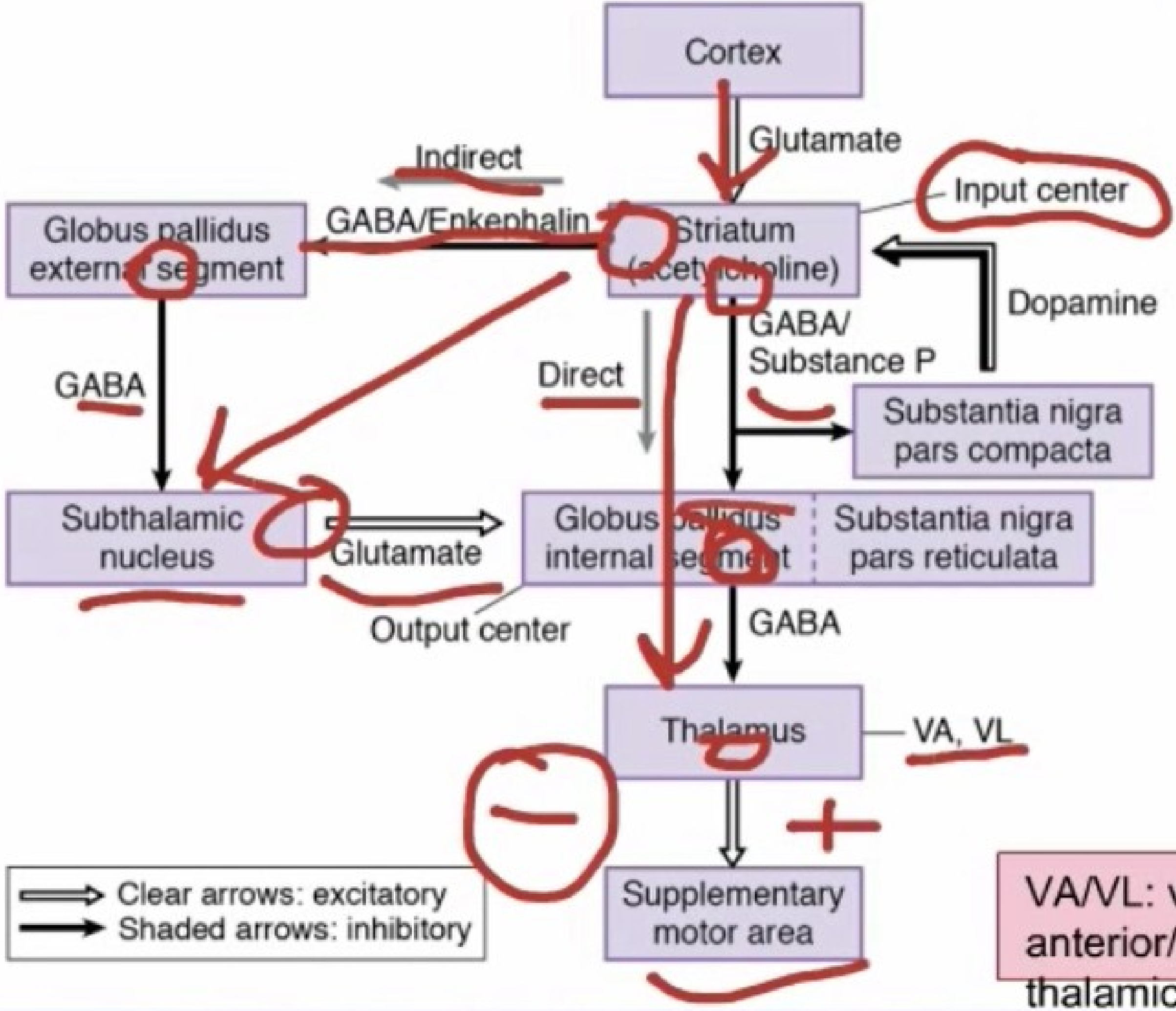
Basal Ganglia Pathways

Note
Both basal ganglia pathways utilize 2 GABA neurons in series, and a “disinhibition”



Note
- Dopamine drives the direct pathway
- Acetylcholine (ACh) drives the indirect pathway

Direct Pathway:
Drives motor cortex- promotes Movement
Enhanced by DOPA

Indirect Pathway:
Inhibits motor cortex-suppresses movement
Enhanced by ACh

VA/VL: ventral anterior/ventral lateral thalamic nuclei

Figure III-7-2.

RESOURCES
RESOURCES

amiha complains that **her muscles feel stiff**

When asked to walk she is a little slow to get started, short steppage slow shuffling with propulsion and has difficulty stopping and turning.

3-

Explain the gait of Samiha?

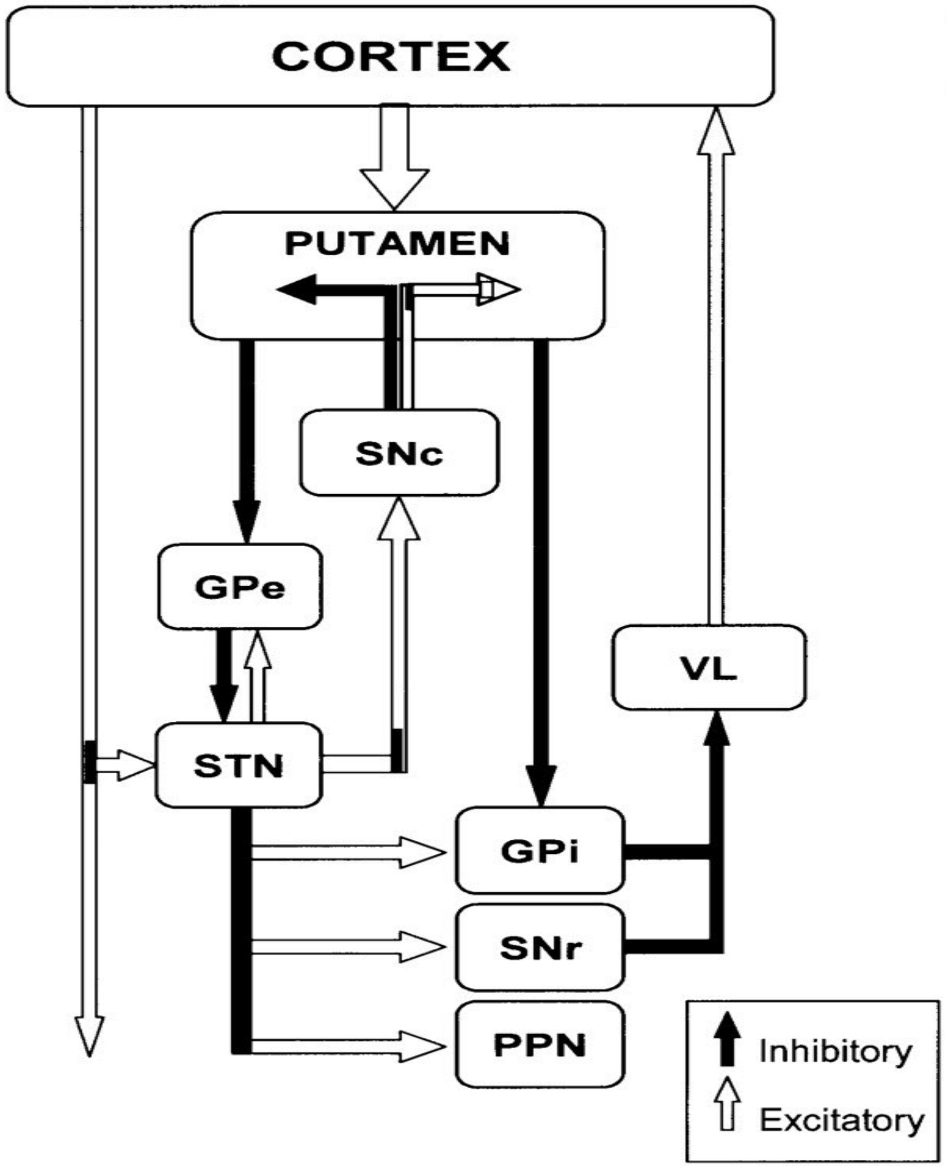
Role of substantia nigra in movement initiation

- Dopamine (from nigro-striatal fibers) excites the direct pathway (facilitatory) and inhibits the indirect pathway (inhibitory).

- So its net effect to increase facilitatory inputs to the motor regions.

- Loss of this dopaminergic influence renders initiation abnormally difficult (slow to start = hypokinesia).

NORMAL MOTOR CIRCUIT



CORTEX

PUTAMEN

SNc

GPe

STN

VL

GPi

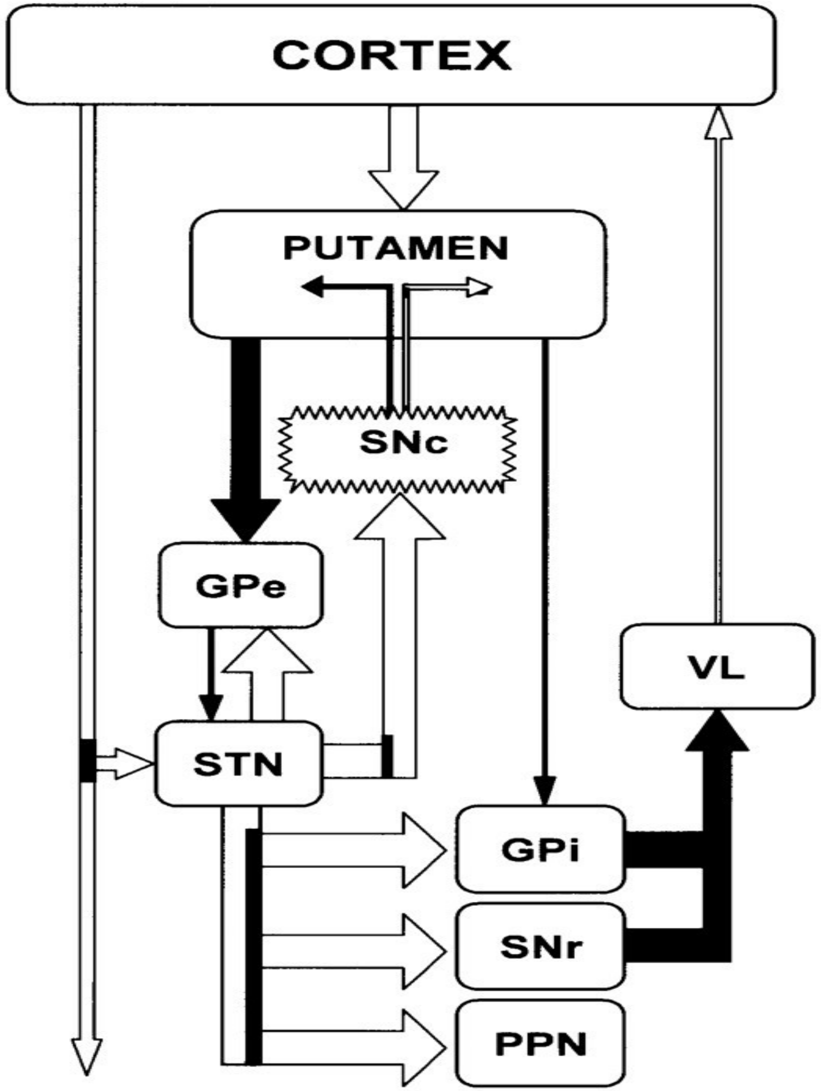
SNr

PPN

Inhibitory

Excitatory

MOTOR CIRCUIT IN PD



CORTEX

PUTAMEN

SNc

GPe

STN

VL

GPi

SNr

PPN

Explain the muscle stiffness in Samiha

Role of substantia nigra in muscle tone.

- The net effect of basal ganglia on muscle tone is inhibitory (ie. Basal ganglia inhibit the motor neurons)

- In Parkinson’s disease, rigidity is due to increased both Alpha & Gamma motor neuron discharge due to decreased inhibitory impulses.

- This rigidity in the antagonistic muscle groups limits the range of stepping, causing small shuffling steps.

What is the neurotransmitter in the affected area?

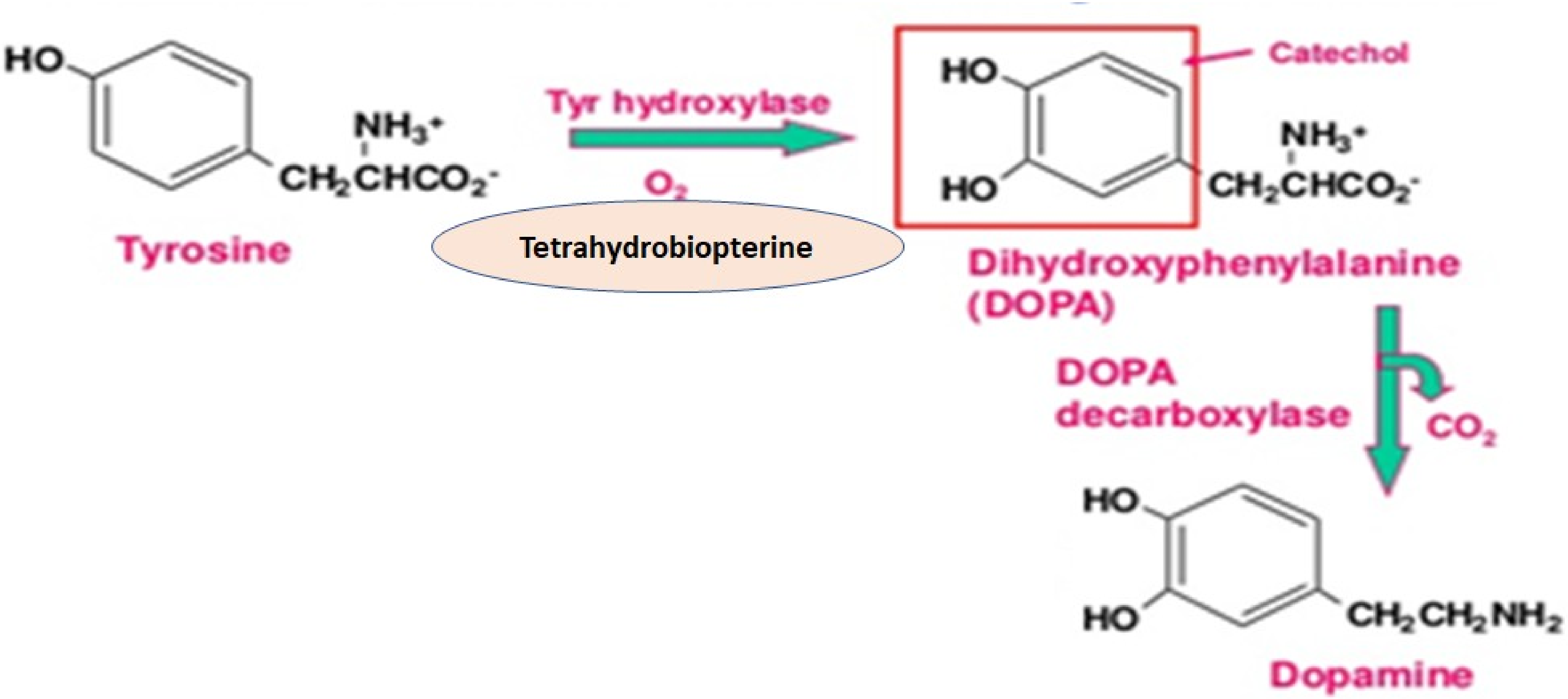
Substantia Nigra (pars compacta)

Dopamine

4- Mention the steps of dopamine biosynthesis

What is the end product of its catabolism?

Biosynthesis of Dopamine

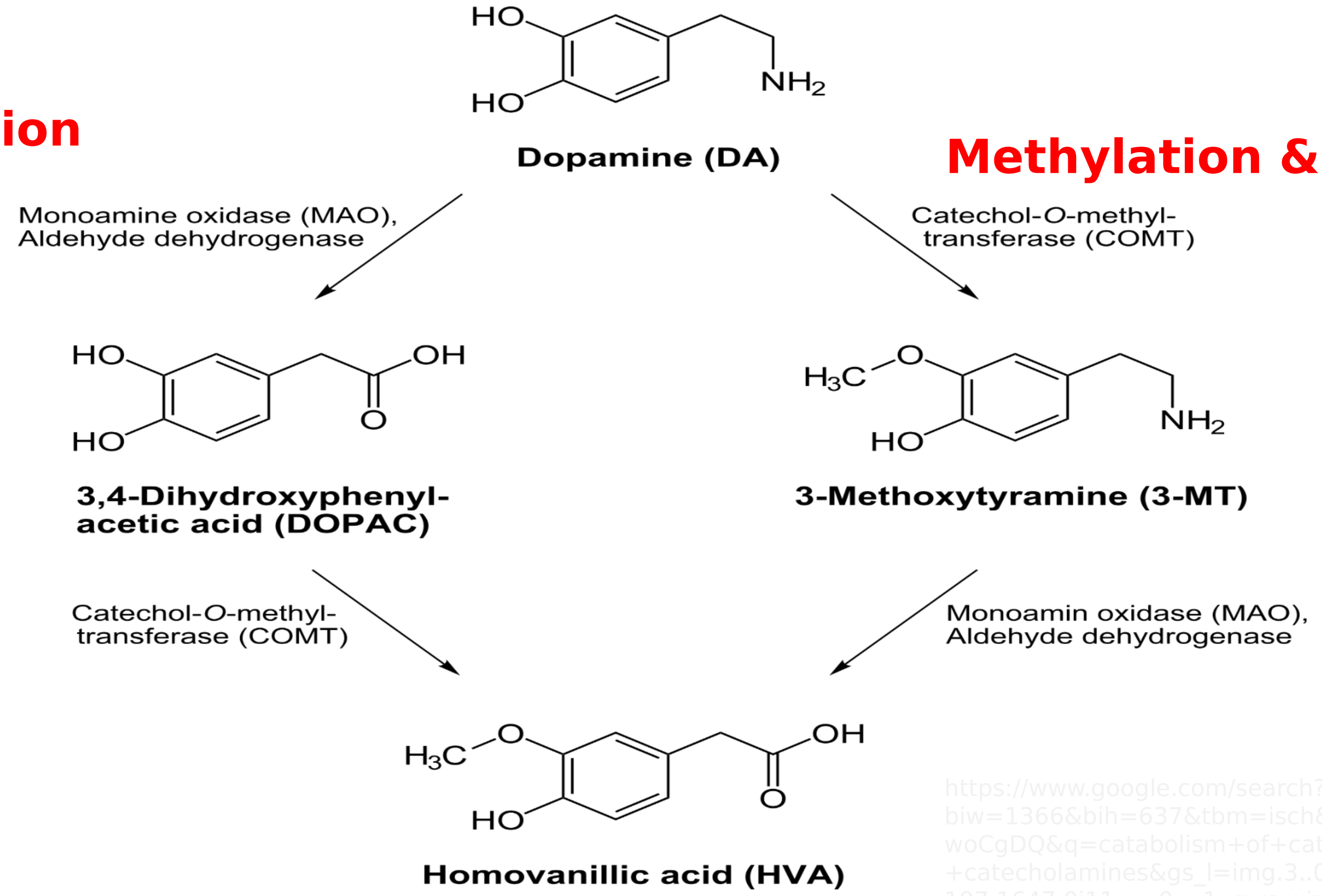


Catabolism to biologically inactive products:

A) Catabolism of dopamine

Oxidative Deamination & Inactivation

Methylation & inactivation



https://www.google.com/search?biw=1366&bih=637&tbm=isch&sa=1&ei=Q-zPXd2sLay_lwS-woCgDQ&q=catabolism+of+catecholamines&oq=catabolism+of+catecholamines&gs_l=img.3..0i19.55442.58665..58920...0.0..0.197.1647.0j11......0....1..gws-wiz-img.......0i7i30._KwGe9sDZ-c&ved=0ahUKEwid2vK23u7lAhWs34UKHT4hANQQ4dUDCAc&uact

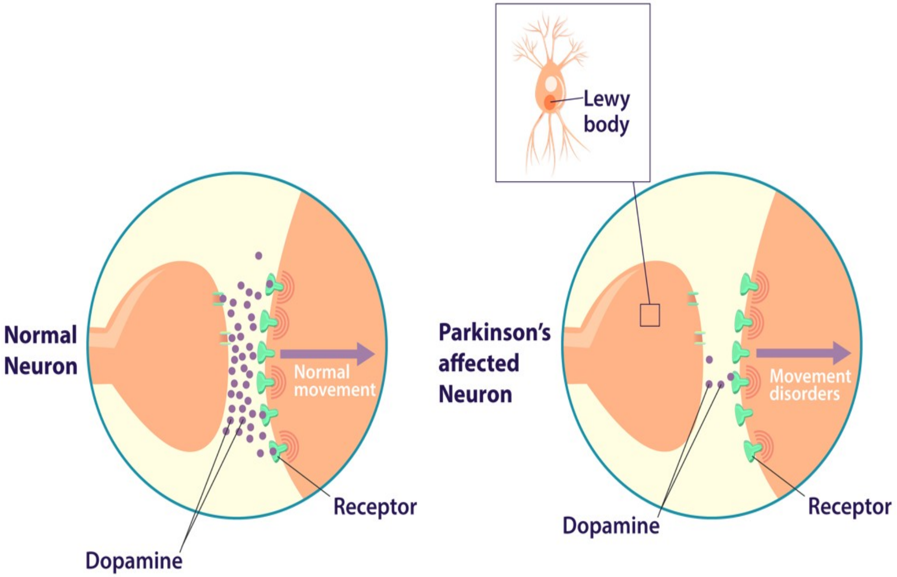
5- Mention the pathogenesis of Parkinson’s disease

PD is a **neurodegenerative disease**, associated with characteristic **neuronal inclusions containing α-synuclein protein** .

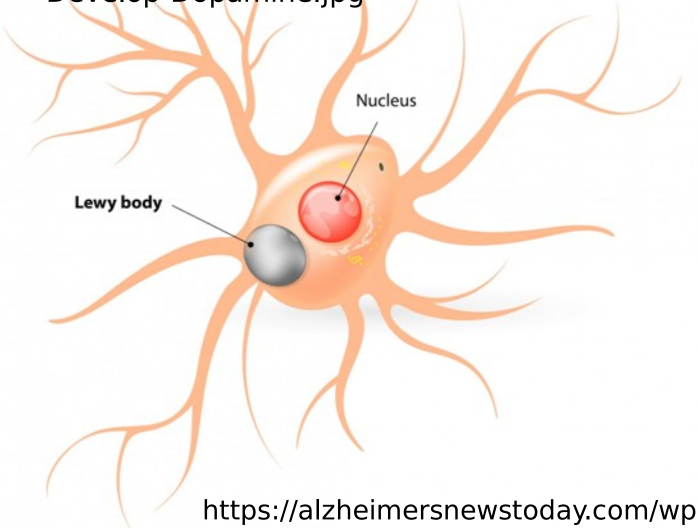
- **The *SNCA* gene (alpha-synuclein)** h been identified as a risk factor which is involved in synaptic transmission.

- ***SNCA gene*** mutations and multiplications are associated with **familial PD**, but the **majority** of cases are **sporadic**.

- Even in sporadic PD, the diagnostic feature of the disease is the **Lewy body**



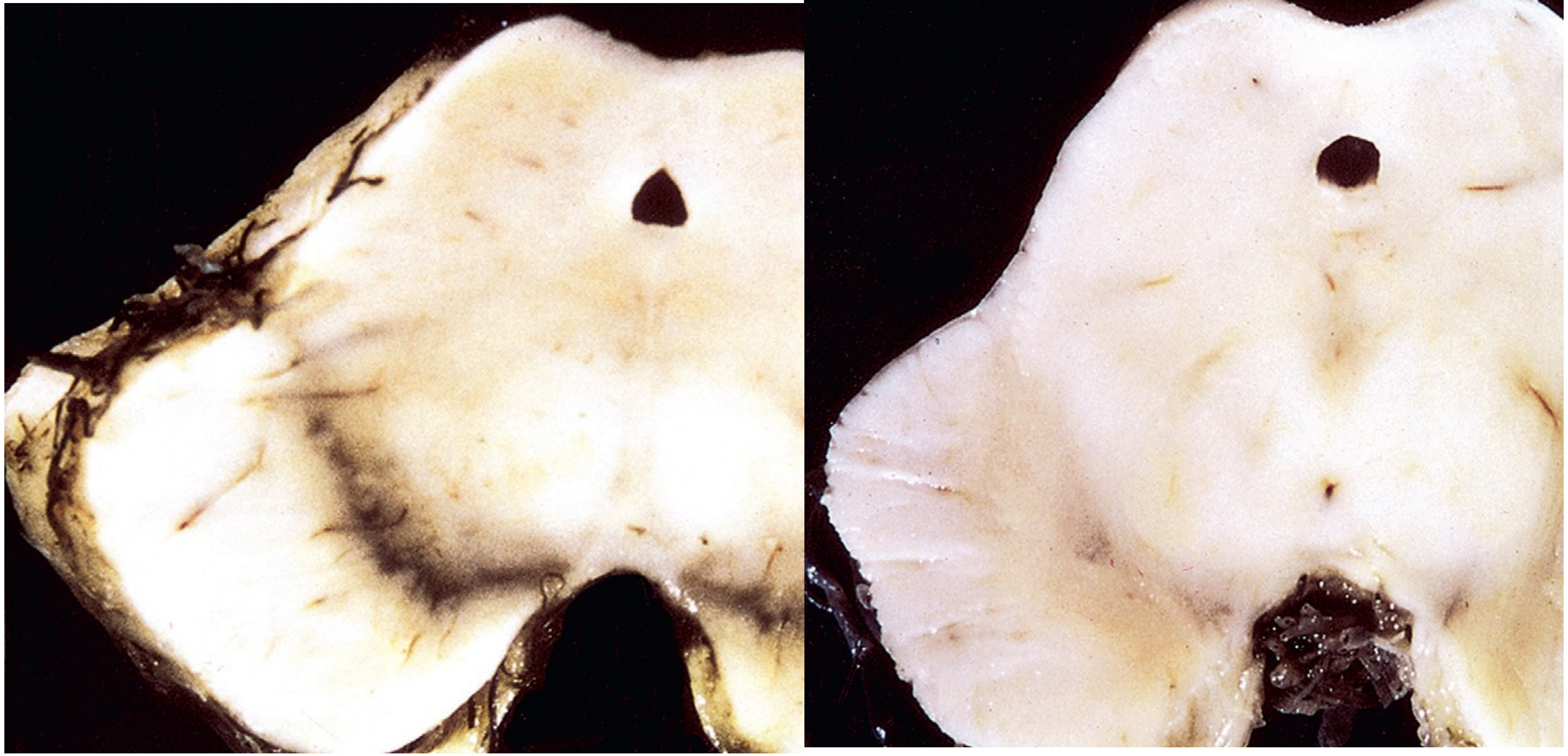
https://parkinsonsdisease.net/wp-content/uploads/2017/04/How-Does-Parkinson%E2%80%99s-Disease-Develop-Dopamine.jpg



https://alzheimersnewstoday.com/wp-content/uploads/2014/12/shutterstock_227273575.jpg

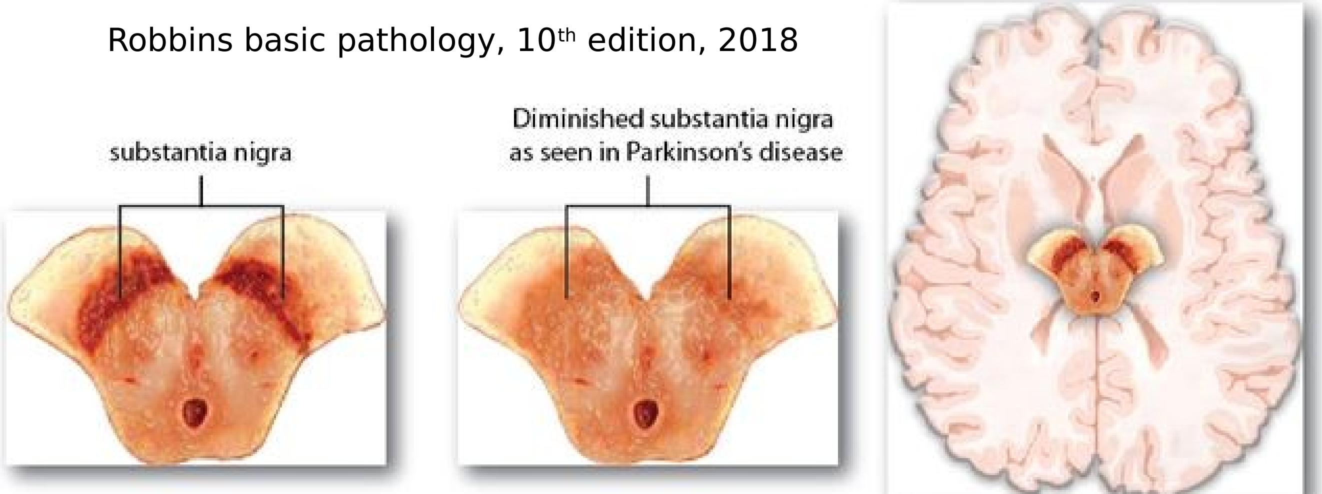
Describe Gross and Microscopic picture in Parkinson’s disease

Gross picture: There is **pallor** of the **substantia nigra**.



A) Normal substantia nigra. B) Depigmented substantia nigra in idiopathic Parkinson disease.

Robbins basic pathology, 10th edition, 2018

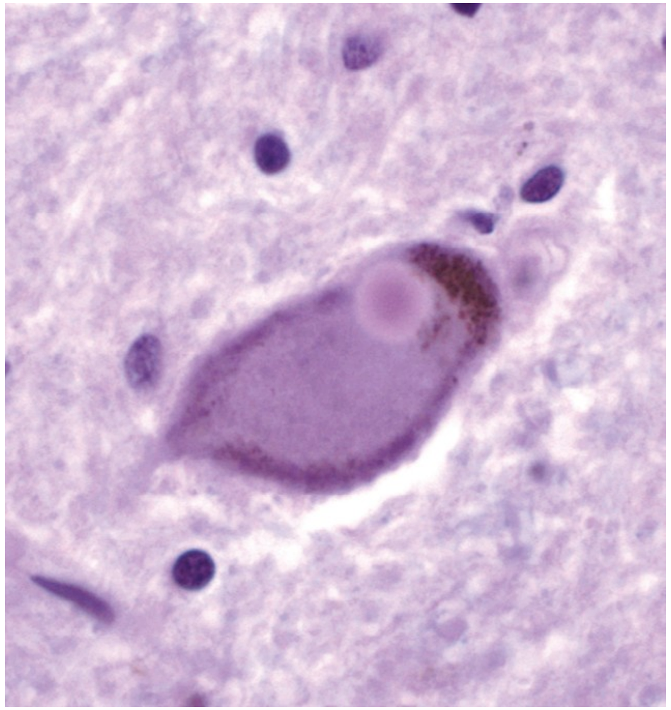


Parkinson Disease

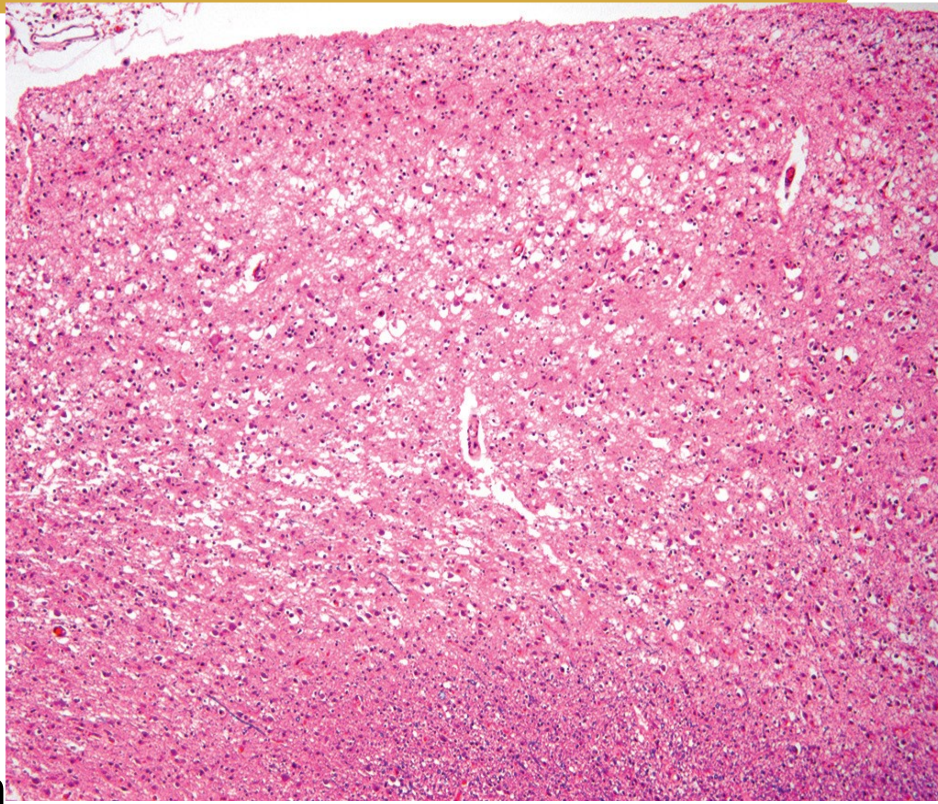
Microscopic examination:

1- **Loss** of pigmented **(dopaminergic) neurons** in the substantia nigra associated with gliosis.

2- Residual neurons show: **Lewy bodies**, which are **intracytoplasmic**



Lewy body in a neuron from the substantia nigra stains pink.



Severe neuronal loss and gliosis in the region of

Robbins basic pathology, 10th edition, 2018

6- Is the drug history important in Samiha?

It is important for:

Drug induced parkinsonism:

- **Antipsychotics**: block D2 receptors
- **Reserpine**: antihypertensive drug that depletes DA stores
- **Methyl dopa**: antihypertensive drug that ↓ DA synthesis
- **Metoclopramide:** blocks DA receptors both peripherally and centrally

Suggest the needed investigations to be done?

- General speaking, PD is a neurodegenerative disorder, it is diagnosed by **clinical examination** mainly with **no further investigation is needed**.

- Investigations could be done if **secondary cause** is suspected e.g infarction. (ask for CT or MRI)

- SPECT scan could be requested if the clinician is confused whether it is idiopathic PD or secondary (e.g due to anti dopaminergic drug intake) or psychogenic. PET is positive only in the idiopathic PD and it shows diminished dopaminergic function in basal ganglia.

Welcome Back

Stiff muscle with hand shaking

MRI and SPECT scan were done. SPECT showed diminished dopaminergic function in basal ganglia

The doctor let Samiha started treatment with:

Dopamine agonist **Pramipexole (Ramixole).**

After 1 month, there was **no** obvious improvement apart from mild improvement of tremors

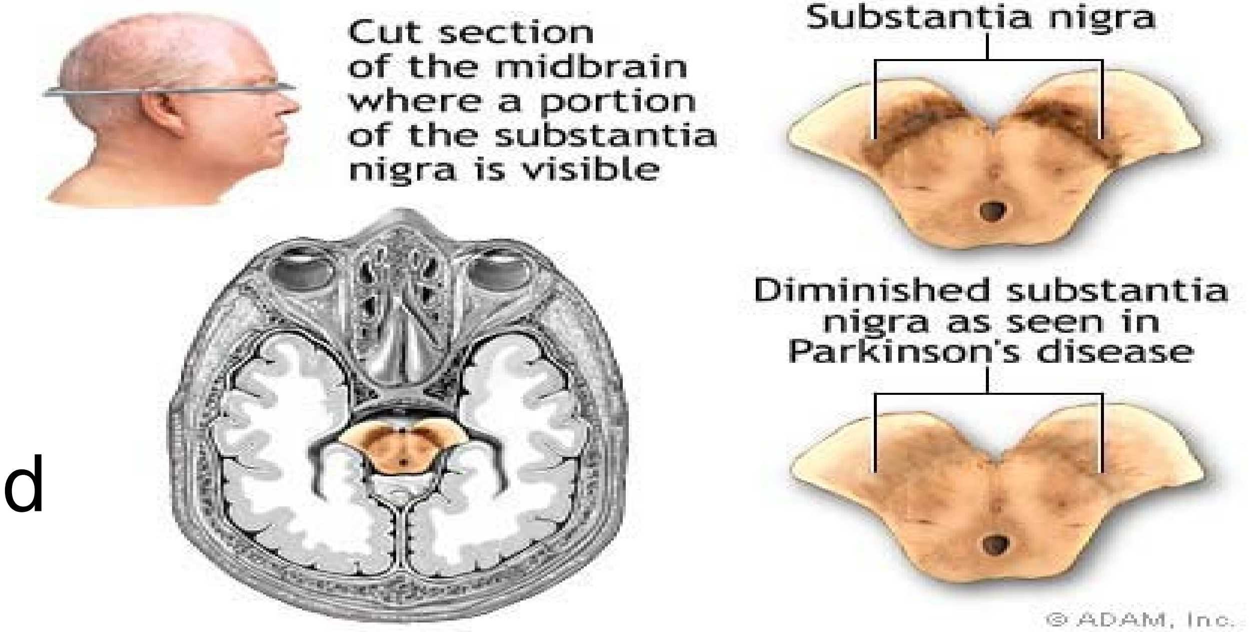
So, the doctor prescribed **Carbidopa/levodopa (Sinemet 25mg/ 100mg).** There was a **significant improvement of bradykinesia** and rigidity.

Also, **antidepressant Sertraline (Lustral)** was added for treatment of depression with marked improvement over the next 2 months.

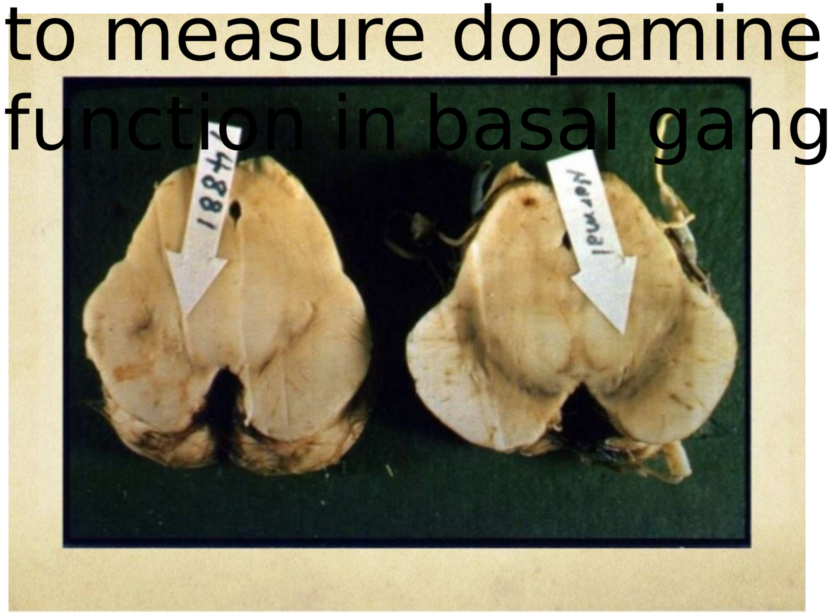
SPECT showed diminished dopaminergic function in basal ganglia.

Interpret the Results

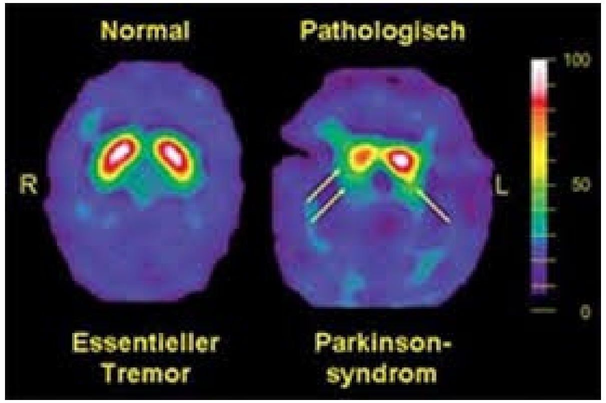
MRI usually normal but may exclude other causes of **parkinsonism** **e.g vascular causes and tumors**.

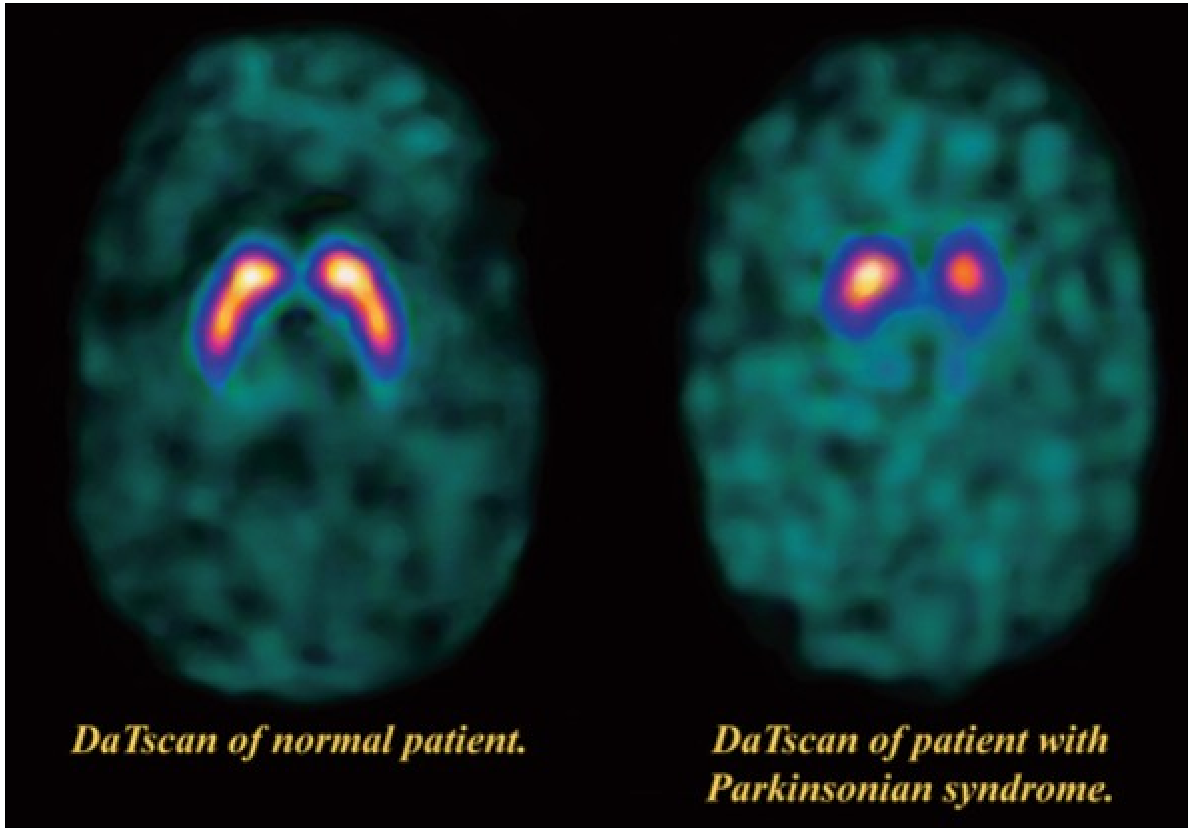

Cut section of the midbrain where a portion of the substantia nigra is visible
Substantia nigra
Diminished substantia nigra as seen in Parkinson's disease
© ADAM, Inc.

PET / SPECT scans can be used to measure dopaminergic function in basal ganglia.



Loss of **dopaminergic** neurons in the **substantia nigra**





DaTscan of normal patient.

DaTscan of patient with Parkinsonian syndrome.

7- Classify the antiparkinsonian drugs according to their mechanism of action

↑ DA

- **Levodopa/carbidopa.**
- **DA agonists**
  - (ergot): Bromocriptine
  - (non-ergot): Pramipexole
- **Amantadine**.
- **COMT inhibitors:**Entacapone.
- **MAO-B inhibitors:**Selegiline-Rasagiline.

↓ Ach

- **Anticholinergics**:
- Benztropine Especially for tremors
- **Why anticholinergic is not preferable to use ?**

I) Dopaminergic drugs

Most effective

Levo dopa/ Carbidopa

Main stay of therapy

Mechanism of action:

Levo dopa

- An immediate **precursor of DA** which **crosses BBB** (DA can not) converted **centrally** via **Dopa Decarboxylase (DD)** enzyme into **DA**.

Carbidopa

- Without *carbidopa*, much of levodopa is decarboxylated to DA in the periphery, resulting in peripheral adverse effects.
- **Carbidopa**, a **peripheral Dopa Decarboxylase enzyme** inhibitor → ↓ levodopa metabolism peripherally → ↑ its availability centrally.

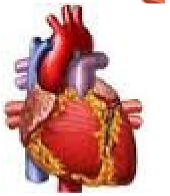
8- What are the Advantages of combination of carbidopa with levodopa?

Advantages of combination of carbidopa with levodopa:

- Lowers the daily dose of levodopa by four- to fivefold
- Decreases the severity of the peripheral side effects
- Increases the central effect

9- What are the adverse effects of levodopa?

Adverse effects of levodopa:



A) Peripheral(↓with carbidopa)

- GIT: nausea, and vomiting,□HCl (# PU)
- CVS: arrhythmias(# ISHD)

B) Central(↑with carbidopa)

- Confusion, Hallucinations, psychosis
- dyskinesias

C) Fluctuations in response

- End of dose akinesia
- On-off effect

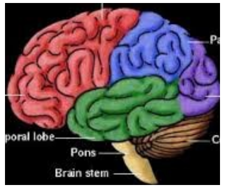
What are the adverse effects of Dopamine agonists, Amantadine, Mao-B inhibitors and COMT inhibitors ?

Dopaminergic agonists
Adverse effects:

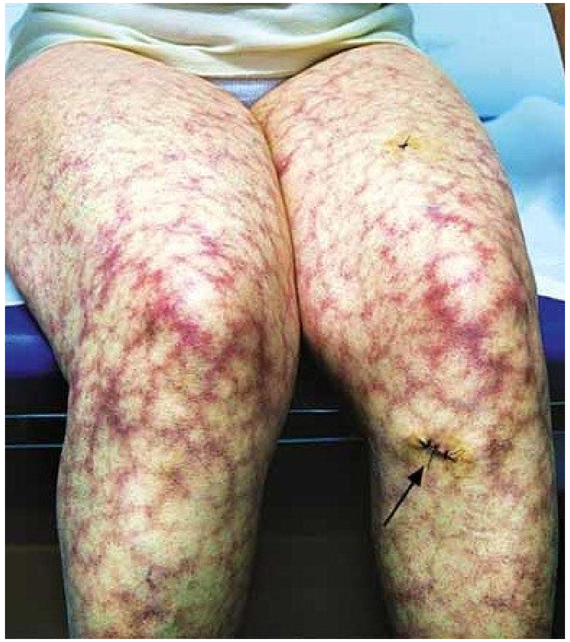
Ergot Bromocriptine	**Non ergot** Pramipexole
- As L-dopa but ↓dyskinesia & ↑ hallucinations - Nausea, postural hypotension - Ergot derivative → - 1- vasospasm - 2- cardiac fibrosis	- As L-dopa but ↓dyskinesia & ↑ hallucinations - less

Amantadine

Adverse effects:



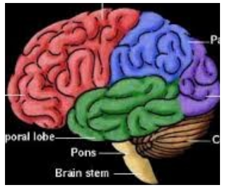
- Hallucinations
- Insomnia
- peripheral edema
- Livedo reticularis



- Amantadine is less efficacious than levodopa
- **Tolerance** develops more readily.

MAO-BIs (selegline)

Adverse effects:



- Dizziness , lightheadedness, hallucinations
- low risk of cheese reaction (hypertensive crisis) in usual doses , higher dose increase the risk

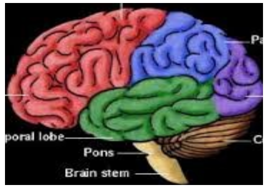
Drug interactions:

Selegiline should not be coadministered with:

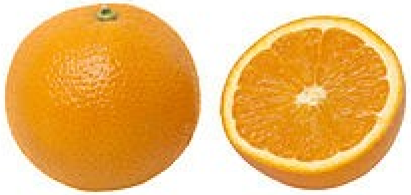
1) Tricyclic antidepressants
2) Selective serotonin uptake inhibitors

COMT-I Entacapone

Adverse effects:



- Orange urine
- Unwanted /uncontrolled movements



10- How could you manage PD?

In general, treatment of PD can be divided into

management of **__motor__** symptoms

management of **__non motor__** symptoms

- The initial drug of choice in managing **motor symptoms** will vary between patients and will depend on different factors:

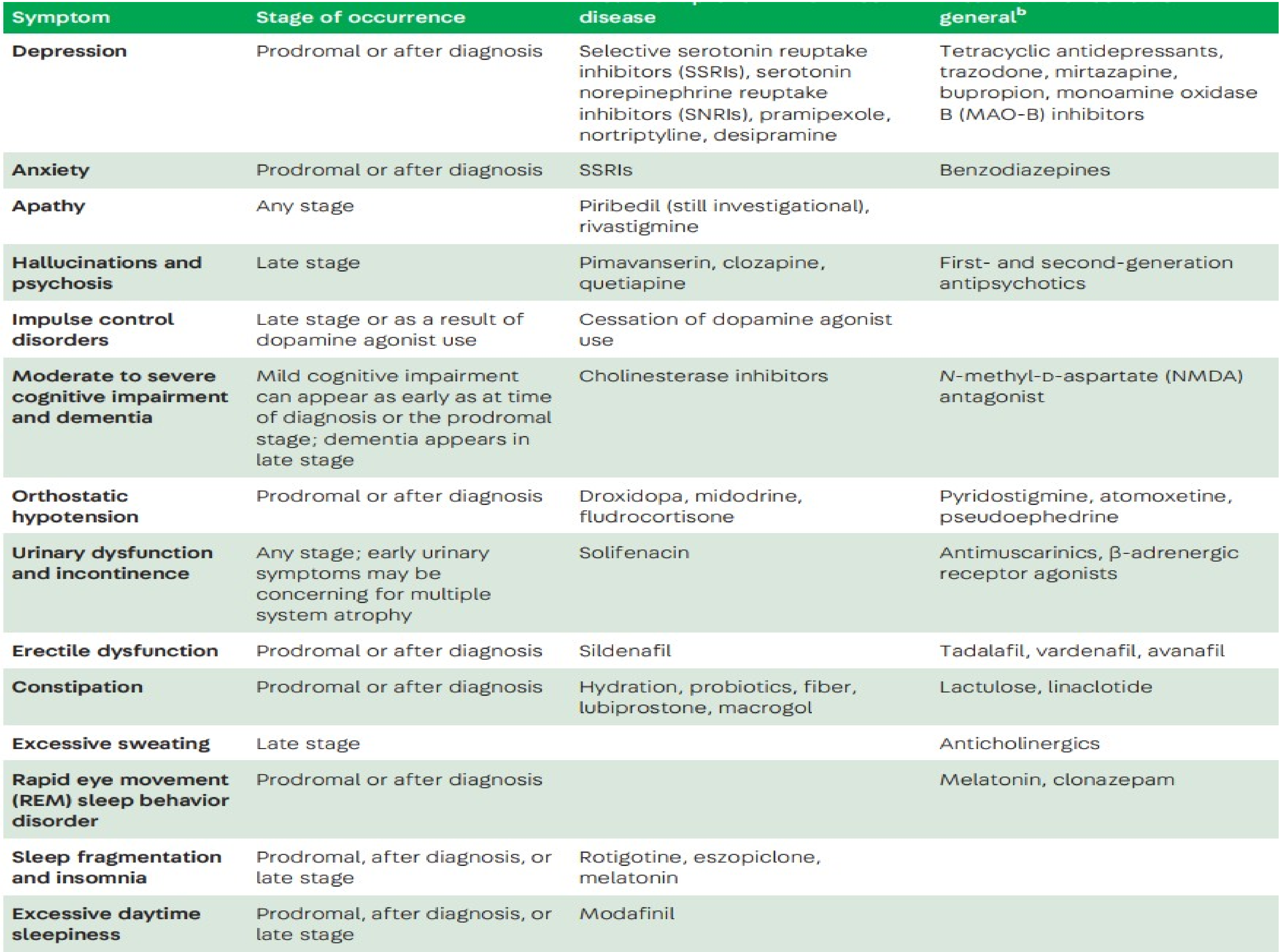
1- Age of the patient: Young patient you may **try DA first**

2- Old patient be **aware of anticholinergic side effects** of certain drugs.

3- Comorbid condition: e.g hallucinations: be aware of dopaminergic side effects

4- Sinemet fluctuation or decreased efficacy try Stalevo

Medication class	Dosage	Indication	Adverse effect
Levodopa/Carbidopa and Levodopa/ Benserazide	Titrate to initial dose of 100/25 mg thrice daily; max dose is variable, depending on tolerability	All motor symptoms	Nausea, orthostatic hypotension, dyskinesia, and hallucinations
Pramipexole*	Start 0.125 mg thrice daily; max, 4.5 mg/day	All motor symptoms	Nausea, orthostatic hypotension, psychosis, ICDs, edema, and sleepiness (including sleep attacks)
Ropinirole*	Start 0.25 mg thrice daily; max, 24 mg/day	All motor symptoms	Same as pramipexole
Rotigotine	Start 2 mg/24 h; max, 16 mg/24 h	All motor symptoms	Same as pramipexole plus skin reactions
Entacapone	200 mg with each dose of levodopa; max, 8/day	Motor fluctuations	Dark-colored urine and exacerbation of levodopa adverse effects
Tolcapone	100–200 mg thrice daily	Motor fluctuations resistant to entacapone	Same as entacapone, plus hepatotoxicity
Selegiline	5–10 mg daily	Early, mild motor symptoms and fluctuations	Stimulant effect, dizziness, headache, exacerbation of levodopa adverse effects
Rasagiline	0.5–1 mg daily	Early, mild motor symptoms and fluctuations	Headache, arthralgia, dyspepsia, flu-like syndrome, exacerbation of levodopa adverse effects, and constipation
Amantadine	100–300 mg daily, max 400 mg daily	Dyskinesia	Irritability, nightmares, purplish red, net-like spots on the skin
Apomorphine	Max 100 mg daily	Motor fluctuations	Same as pramipexole plus side effects associated with infusion
Intrajejunal levodopa carbidopa gel (Duodopa®)	Max 200 mL daily	Motor fluctuations	Same as levodopa plus side effects associated with infusion



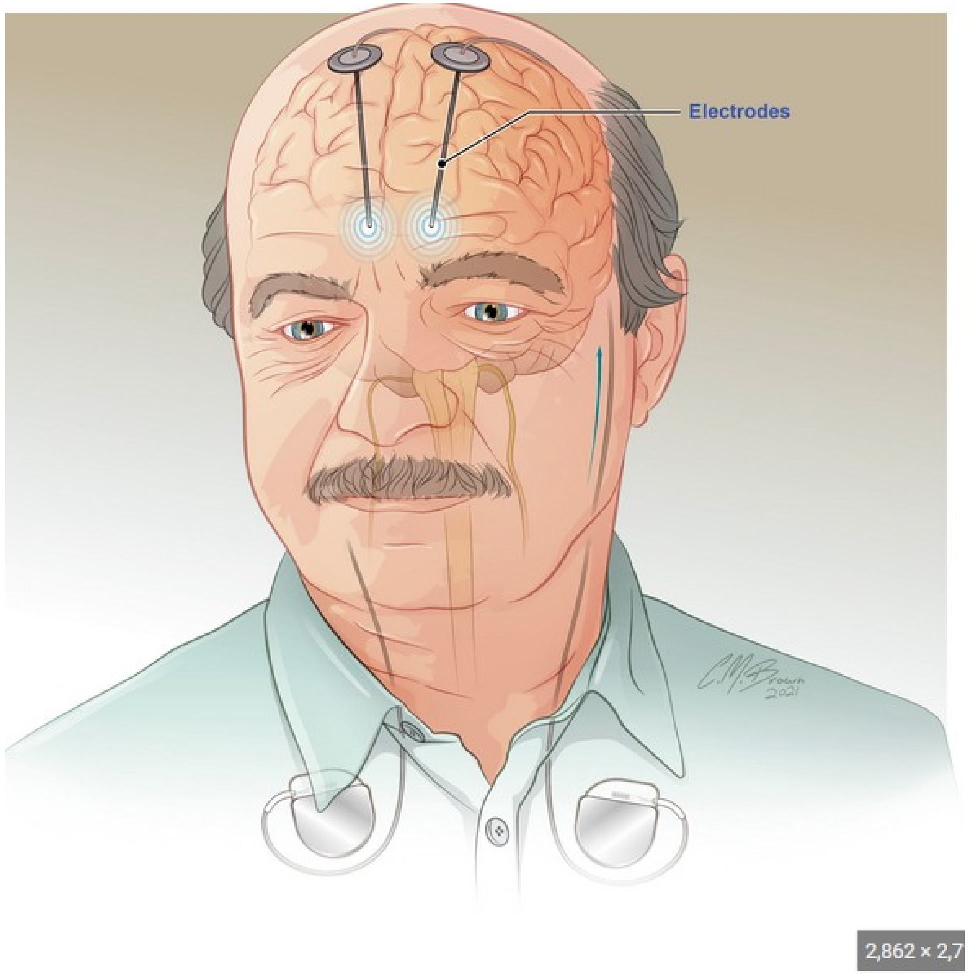
Symptom	Stage of occurrence	disease	general[b]
Depression	Prodromal or after diagnosis	Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), pramipexole, nortriptyline, desipramine	Tetracyclic antidepressants, trazodone, mirtazapine, bupropion, monoamine oxidase B (MAO-B) inhibitors
Anxiety	Prodromal or after diagnosis	SSRIs	Benzodiazepines
Apathy	Any stage	Piribedil (still investigational), rivastigmine	
Hallucinations and psychosis	Late stage	Pimavanserin, clozapine, quetiapine	First- and second-generation antipsychotics
Impulse control disorders	Late stage or as a result of dopamine agonist use	Cessation of dopamine agonist use	
Moderate to severe cognitive impairment and dementia	Mild cognitive impairment can appear as early as at time of diagnosis or the prodromal stage; dementia appears in late stage	Cholinesterase inhibitors	*N*-methyl-ᴅ-aspartate (NMDA) antagonist
Orthostatic hypotension	Prodromal or after diagnosis	Droxidopa, midodrine, fludrocortisone	Pyridostigmine, atomoxetine, pseudoephedrine
Urinary dysfunction and incontinence	Any stage; early urinary symptoms may be concerning for multiple system atrophy	Solifenacin	Antimuscarinics, β-adrenergic receptor agonists
Erectile dysfunction	Prodromal or after diagnosis	Sildenafil	Tadalafil, vardenafil, avanafil
Constipation	Prodromal or after diagnosis	Hydration, probiotics, fiber, lubiprostone, macrogol	Lactulose, linaclotide
Excessive sweating	Late stage		Anticholinergics
Rapid eye movement (REM) sleep behavior disorder	Prodromal or after diagnosis		Melatonin, clonazepam
Sleep fragmentation and insomnia	Prodromal, after diagnosis, or late stage	Rotigotine, eszopiclone, melatonin	
Excessive daytime sleepiness	Prodromal, after diagnosis, or late stage	Modafinil	

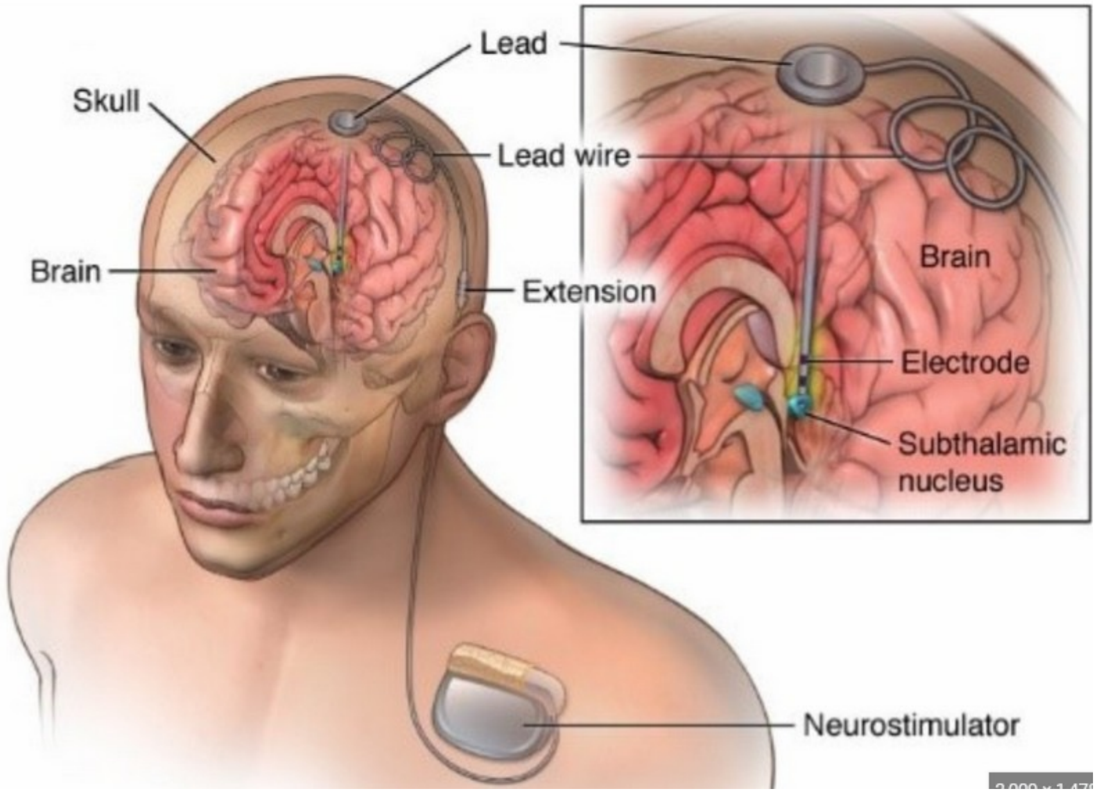
NB:

- Gait and speech will not improve with Sinemet. The patient will need physiotherapy and speech therapy.

- Surgical options of PD include:

- deep brain stimulation
- Levodopa pump
- Apomorphine pump
- (OLD) Cauterization of STN (subthalamotomy or pallidotomy)


Electrodes
C.M. Brown 2021
2,862 × 2,7


Lead
Skull
Lead wire
Brain
Extension
Brain
Electrode
Subthalamic nucleus
Neurostimulator

Take Home Messages

- Parkinson’s disease is a systemic disease selective to dopaminergic neurons in the CNS, yet other causes as subdural hematoma, stroke and tumor should be excluded.

- Antidepressants and antipsychotics choice in Parkinson’s patients should be chosen carefully not to increase symptoms or cause delerium

THANK
YOU